* The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 14:06:55 ON 30 OCT 2005

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 14:07:04 ON 30 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 OCT 2005 HIGHEST RN 866391-97-1
DICTIONARY FILE UPDATES: 28 OCT 2005 HIGHEST RN 866391-97-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

**********
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
**********

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1626GMS

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

| | | |
|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | JUL 20 | Powerful new interactive analysis and visualization software, STN AnaVist, now available |
| NEWS 4 | AUG 11 | STN AnaVist workshops to be held in North America |
| NEWS 5 | AUG 30 | CA/CAplus -Increased access to 19th century research documents |
| NEWS 6 | AUG 30 | CASREACT - Enhanced with displayable reaction conditions |
| NEWS 7 | SEP 09 | ACD predicted properties enhanced in REGISTRY/ZREGISTRY |
| NEWS 8 | OCT 03 | MATHDI removed from STN |
| NEWS 9 | OCT 04 | CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices |
| NEWS 10 | OCT 06 | STN AnaVist workshops to be held in North America |
| NEWS 11 | OCT 13 | New CAS Information Use Policies Effective October 17, 2005 |
| NEWS 12 | OCT 17 | STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools |
| NEWS 13 | OCT 27 | Free KWIC format extended in full-text databases |
| NEWS 14 | OCT 27 | DIOGENES content streamlined |
| NEWS 15 | OCT 27 | EPFULL enhanced with additional content |

| | |
|---|---|
| NEWS EXPRESS | JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005 |
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS INTER | General Internet Information |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS PHONE | Direct Dial and Telecommunication Network Access to STN |
| NEWS WWW | CAS World Wide Web Site (general information) |

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

*PROMT - PROMT from 1978 - present

```
=> S L1
SAMPLE SEARCH INITIATED 14:07:18 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      105 TO ITERATE

100.0% PROCESSED      105 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1486 TO     2714
PROJECTED ANSWERS:               1 TO       80

L2             1 SEA SSS SAM L1

=> S L1 SSS FULL
FULL SEARCH INITIATED 14:07:25 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     1855 TO ITERATE

100.0% PROCESSED     1855 ITERATIONS                               28 ANSWERS
SEARCH TIME: 00.00.01

L3            28 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              161.33     161.54

FILE 'HCAPLUS' ENTERED AT 14:07:31 ON 30 OCT 2005
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FILE COVERS 1907 - 30 Oct 2005  VOL 143 ISS 19
FILE LAST UPDATED: 28 Oct 2005  (20051028/ED)

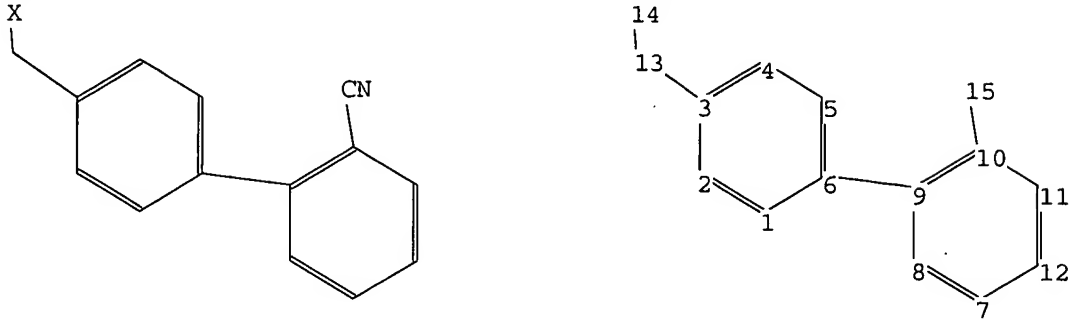
New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> S L3
L4            231 L3

=> FIL REGISTRY
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
```

=>
Uploading C:\Program Files\Stnexp\Queries\10802142.str

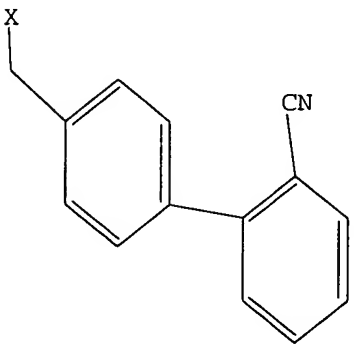



chain nodes :
13 14 15
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
3-13 6-9 10-15 13-14
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact bonds :
3-13 6-9 10-15 13-14
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
isolated ring systems :
containing 1 : 7 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS

L1 STRUCTURE UPLOADED

=> D L1
L1 HAS NO ANSWERS
L1 STR




Structure attributes must be viewed using STN Express query preparation.

| | ENTRY | SESSION |
|---|---|---|
| FULL ESTIMATED COST | 22.05 | 183.59 |

FILE 'REGISTRY' ENTERED AT 14:12:40 ON 30 OCT 2005


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 OCT 2005 HIGHEST RN 866391-97-1
DICTIONARY FILE UPDATES: 28 OCT 2005 HIGHEST RN 866391-97-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

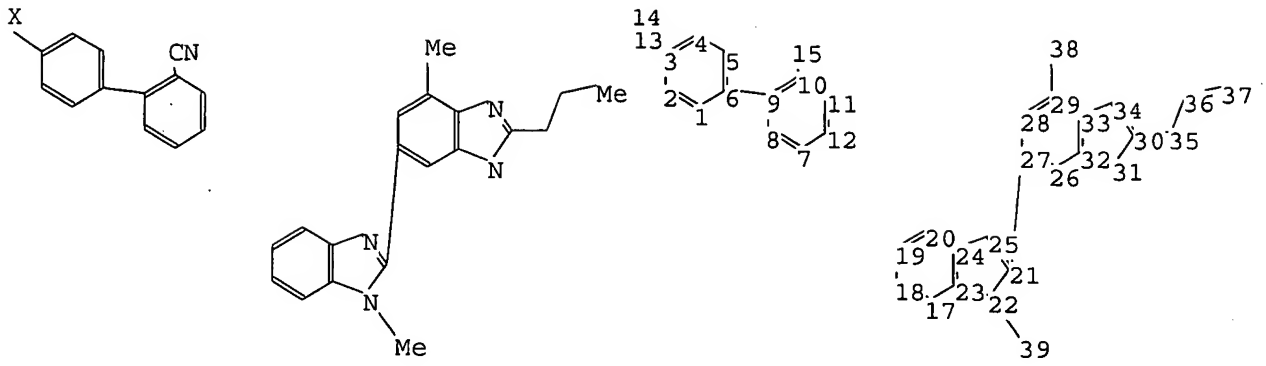
```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10802142a.str



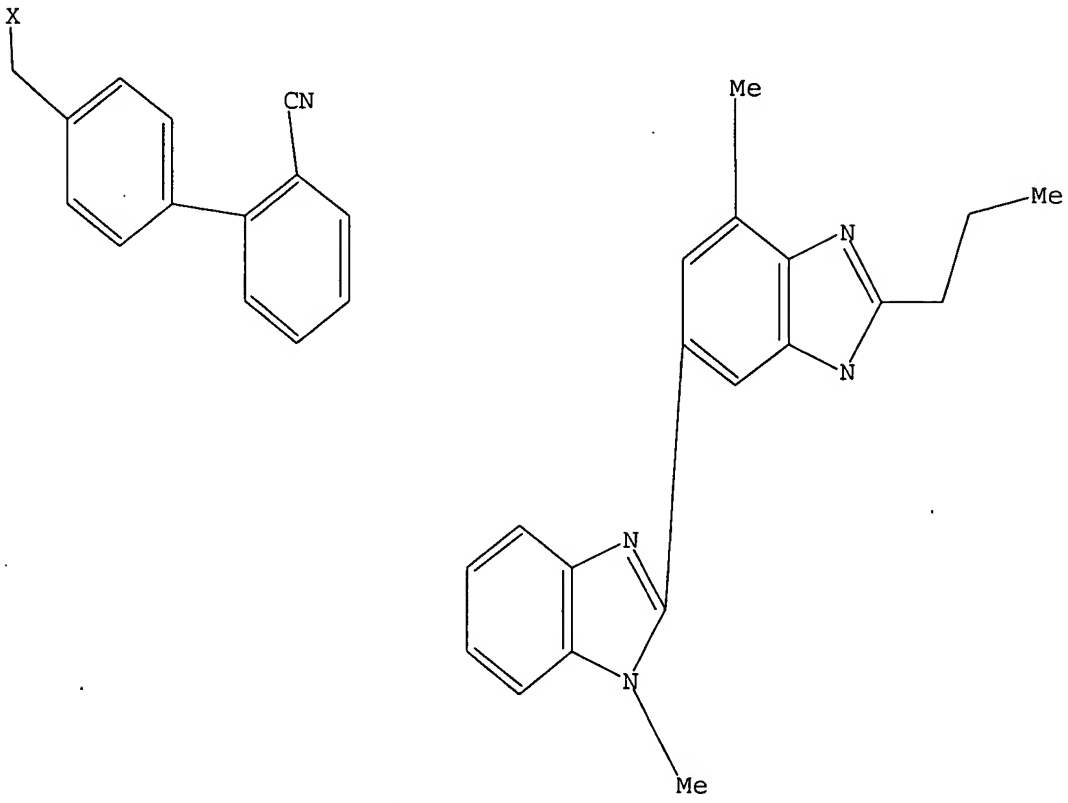

chain nodes :
13 14 15 35 36 37 38 39
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
chain bonds :
3-13 6-9 10-15 13-14 21-27 22-39 29-38 30-35 35-36 36-37
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 17-18 17-23 18-19 19-20 20-24 21-22 21-25 22-23 23-24 24-25 26-27 26-32 27-28 28-29 29-33 30-31 30-34 31-32 32-33 33-34
exact/norm bonds :
21-22 21-25 22-23 24-25 30-31 30-34 31-32 33-34
exact bonds :
3-13 6-9 10-15 13-14 21-27 22-39 29-38 30-35 35-36 36-37
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 17-18 17-23 18-19 19-20 20-24 23-24 26-27 26-32 27-28 28-29 29-33 32-33
isolated ring systems :
containing 1 : 7 : 17 : 26 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 33:Atom 34:Atom 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS

L5 STRUCTURE UPLOADED

```
=> d l6
L6 NOT FOUND
The L-number entered has not been defined in this session, or it
has been deleted.  To see the L-numbers currently defined in this
session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d l5
L5 HAS NO ANSWERS
L5                STR
```




```
Structure attributes must be viewed using STN Express query preparation.


=> s l5
SAMPLE SEARCH INITIATED 14:13:09 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED         1 ITERATIONS                          0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO        80
PROJECTED ANSWERS:               0 TO         0

L6             0 SEA SSS SAM L5

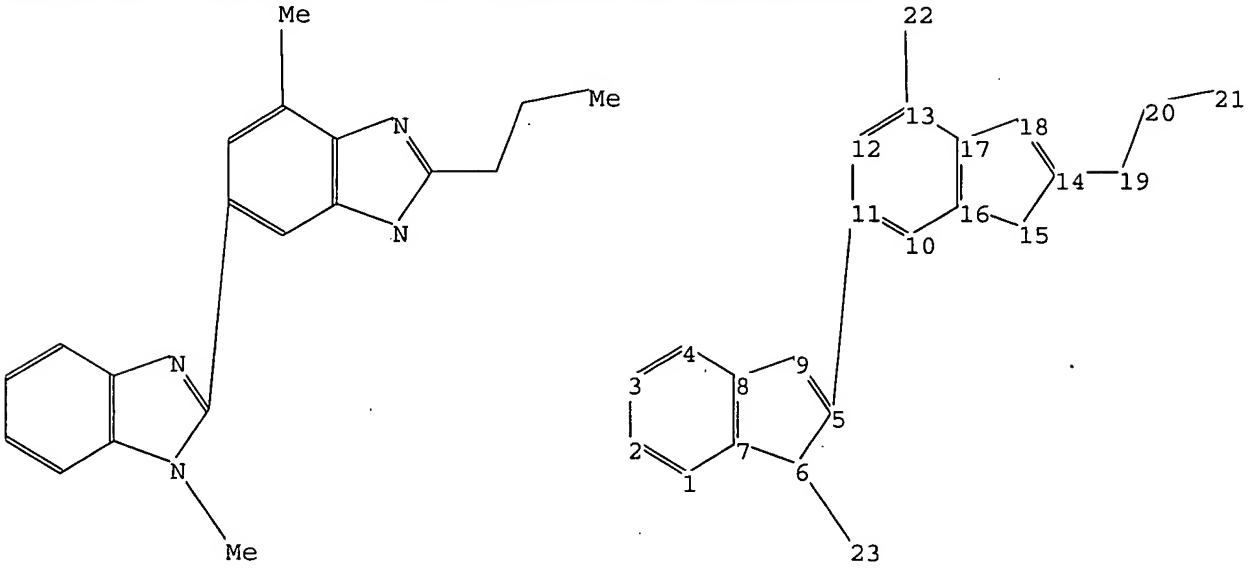
=> s l5 sss full
```

FULL SEARCH INITIATED 14:13:16 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 15 TO ITERATE

100.0% PROCESSED 15 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L7 0 SEA SSS FUL L5

=>
Uploading C:\Program Files\Stnexp\Queries\10802142b.str

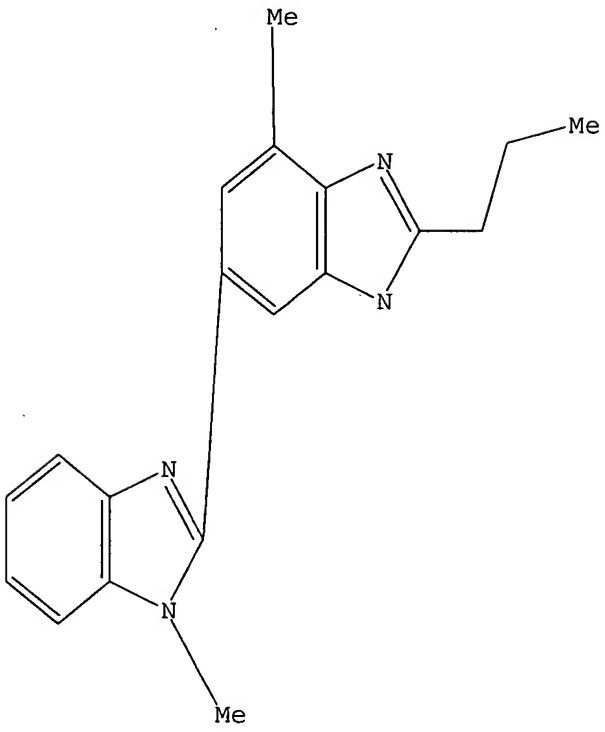



chain nodes :
19 20 21 22 23
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
chain bonds :
5-11 6-23 13-22 14-19 19-20 20-21
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 10-11 10-16 11-12 12-13 13-17
14-15 14-18 15-16 16-17 17-18
exact/norm bonds :
5-6 5-9 6-7 8-9 14-15 14-18 15-16 17-18
exact bonds :
5-11 6-23 13-22 14-19 19-20 20-21
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8 10-11 10-16 11-12 12-13 13-17 16-17

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS

L8 STRUCTURE UPLOADED

=> d l8
L8 HAS NO ANSWERS
L8 STR




Structure attributes must be viewed using STN Express query preparation.

=> s l8
SAMPLE SEARCH INITIATED 14:14:21 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 11 TO ITERATE

100.0% PROCESSED 11 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 22 TO 418
PROJECTED ANSWERS: 4 TO 200

L9 4 SEA SSS SAM L8

=> s l8 sss full
FULL SEARCH INITIATED 14:14:27 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 203 TO ITERATE

100.0% PROCESSED 203 ITERATIONS 97 ANSWERS
SEARCH TIME: 00.00.01

L10 97 SEA SSS FUL L8

```
=> FIL HCAPLUS
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY     SESSION
FULL ESTIMATED COST                                      323.09      506.68

FILE 'HCAPLUS' ENTERED AT 14:14:39 ON 30 OCT 2005
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FILE COVERS 1907 - 30 Oct 2005  VOL 143 ISS 19
FILE LAST UPDATED: 28 Oct 2005  (20051028/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d his

     (FILE 'HOME' ENTERED AT 14:06:55 ON 30 OCT 2005)

     FILE 'REGISTRY' ENTERED AT 14:07:04 ON 30 OCT 2005
L1             STRUCTURE UPLOADED
L2               1 S L1
L3              28 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:07:31 ON 30 OCT 2005
L4             231 S L3

     FILE 'REGISTRY' ENTERED AT 14:12:40 ON 30 OCT 2005
L5             STRUCTURE UPLOADED
L6               0 S L5
L7               0 S L5 SSS FULL
L8             STRUCTURE UPLOADED
L9               4 S L8
L10             97 S L8 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:14:39 ON 30 OCT 2005

=> s l10
L11           397 L10

=> s l4 and l11
L12             3 L4 AND L11

=> s l11 and telmisartan
```

```
            442 TELMISARTAN
L13         375 L11 AND TELMISARTAN

=> s telmisartan
L14         442 TELMISARTAN

=> s l14 and process
       2163817 PROCESS
       1450311 PROCESSES
       3220922 PROCESS
                 (PROCESS OR PROCESSES)
L15         23 L14 AND PROCESS

=> s l4 and l15
L16          0 L4 AND L15

=> s l11 and l15
L17         21 L11 AND L15

=> d his

     (FILE 'HOME' ENTERED AT 14:06:55 ON 30 OCT 2005)

     FILE 'REGISTRY' ENTERED AT 14:07:04 ON 30 OCT 2005
L1              STRUCTURE UPLOADED
L2            1 S L1
L3           28 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:07:31 ON 30 OCT 2005
L4          231 S L3

     FILE 'REGISTRY' ENTERED AT 14:12:40 ON 30 OCT 2005
L5              STRUCTURE UPLOADED
L6            0 S L5
L7            0 S L5 SSS FULL
L8              STRUCTURE UPLOADED
L9            4 S L8
L10          97 S L8 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:14:39 ON 30 OCT 2005
L11         397 S L10
L12           3 S L4 AND L11
L13         375 S L11 AND TELMISARTAN
L14         442 S TELMISARTAN
L15          23 S L14 AND PROCESS
L16           0 S L4 AND L15
L17          21 S L11 AND L15

=> d l12 ibib abs hitstr tot

L12  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:858350  HCAPLUS
DOCUMENT NUMBER:          142:316836
TITLE:                    Preparation of telmisartan
INVENTOR(S):              Shen, Jingshan; Yan, Tiema; Liu, Weisi; Mao, Rui; Li,
                          Jianfeng; Ji, Ruyun
PATENT ASSIGNEE(S):       Shanghai Institute of Pharmacy, Chinese Academy of
                          Sciences, Peop. Rep. China; Tehua Medicine and
                          Chemicals Co., Ltd., Shanghai
```

SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 7 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 1412183 | A | 20030423 | CN 2001-131915 | 20011015 |
| PRIORITY APPLN. INFO.: | | | CN 2001-131915 | 20011015 |

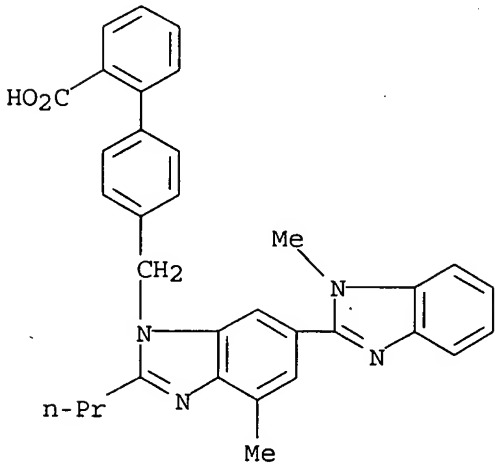
OTHER SOURCE(S): CASREACT 142:316836

AB The method comprises substituting 4-methyl-5-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazole with 4-(2-cyanophenyl)benzyl bromide in solvent in the presence of acid capturing agent at 20-80° for 4-6 h and then hydrolyzing with acid in C1-5 alc.-water or other solvent at 30-160° for 10-20 h. The acid capturing agent is Na alkoxide, triethylamine, tributylamine, tripropylamine, NaOH, KOH, Ca(OH)2, etc. The solvent is DMF, DMSO, THF, dioxane, acetone, etc. The acid is H2SO4, HCl, HBr, and/or glacial acetic acid.

IT **144701-48-4P**, Telmisartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of telmisartan)

RN 144701-48-4 HCAPLUS

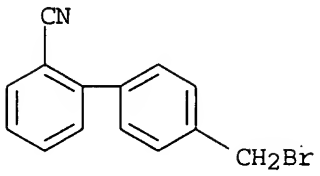
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



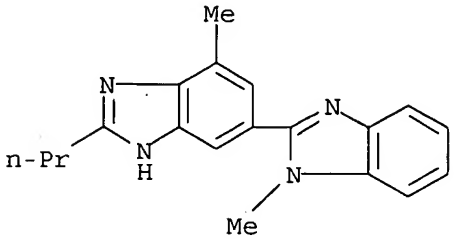

IT **114772-54-2**, 4-(2-Cyanophenyl)benzyl bromide **152628-02-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of telmisartan)

RN 114772-54-2 HCAPLUS

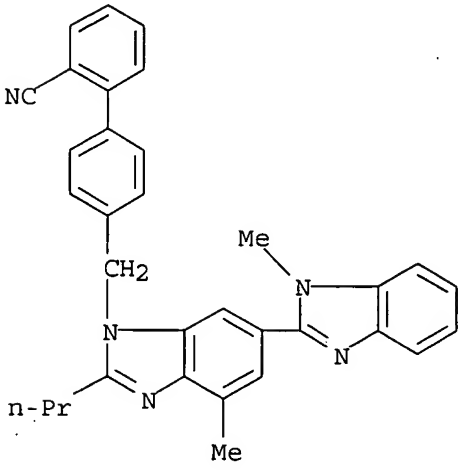
CN [1,1'-Biphenyl]-2-carbonitrile, 4'-(bromomethyl)- (9CI) (CA INDEX NAME)



RN 152628-02-9 HCAPLUS
CN 2,5'-Bi-1H-benzimidazole, 1,7'-dimethyl-2'-propyl- (9CI) (CA INDEX NAME)



IT **144702-27-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of telmisartan)
RN 144702-27-2 HCAPLUS
CN [1,1'-Biphenyl]-2-carbonitrile, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]- (9CI) (CA INDEX NAME)



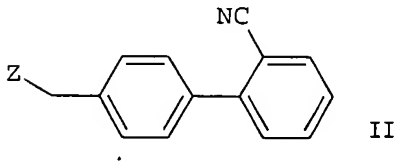
L12 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:857574 HCAPLUS
DOCUMENT NUMBER: 141:332194
TITLE: Preparation of Telmisartan by reaction of 2-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)benzimidazole with 4-bromomethyl-2'-cyanobiphenyl or related compounds followed by hydrolysis.
INVENTOR(S): Hauel, Norbert; Dach, Rolf; Heitger, Helmut; Meyer,

Oliver
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany;
Boehringer Ingelheim Pharma GmbH & Co. Kg
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004087676 | A1 | 20041014 | WO 2004-EP3217 | 20040326 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10314702 | A1 | 20041021 | DE 2003-10314702 | 20030331 |
| US 2004236113 | A1 | 20041125 | US 2004-802142 | 20040317 |

PRIORITY APPLN. INFO.: DE 2003-10314702 A 20030331
US 2003-465952P P 20030428

OTHER SOURCE(S): CASREACT 141:332194; MARPAT 141:332194
GI



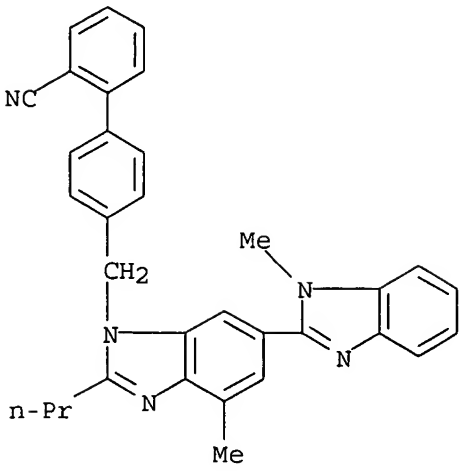

II

AB Telmisartan was prepared by reaction of 2-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)benzimidazole (I) with biphenyl derivative (II; Z = leaving group) followed by hydrolysis. Thus, I was stirred 1 h with KOCMe3 in dimethylacetamide; II (X = Br) in dimethylacetamide was added over 30 min. followed by cooling, removal of solvent in vacuo, and crystn from MeOCMe3 to give 87.5% 2-cyano-4'-[2''-propyl-4''-methyl-6''-(1'''methylbenzimidazol-2'''-yl)benzimidazol-1''-ylmethyl]biphenyl. The latter was hydrolyzed with KOH in ethylene glycol/H2O at 160° for 13.5 h to give after acidification with HCl, 98.2% Telmisartan hydrochloride.

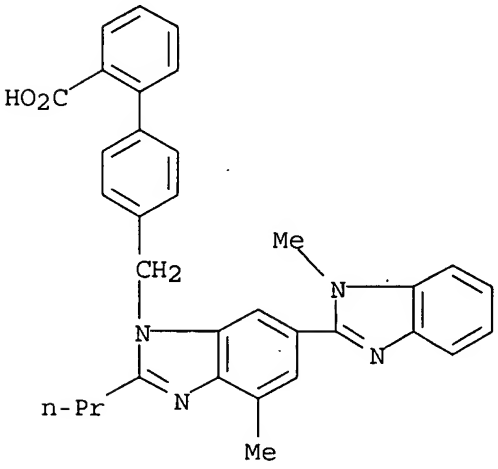
IT **144702-27-2P 515815-48-2P**, Telmisartan hydrochloride
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Telmisartan by reaction of propyldimethylbenzimidazolylbenzimidazole with bromomethylcyanobiphenyl followed by hydrolysis)

RN 144702-27-2 HCAPLUS

CN [1,1'-Biphenyl]-2-carbonitrile, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]- (9CI) (CA INDEX NAME)

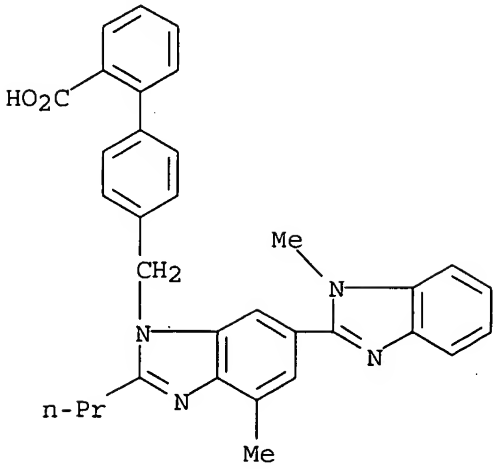


RN 515815-48-2 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, monohydrochloride (9CI) (CA INDEX NAME)

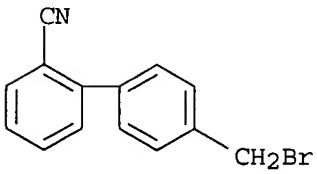


● HCl

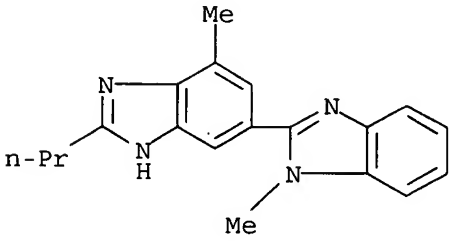
IT **144701-48-4P**, Telmisartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of Telmisartan by reaction of propyldimethylbenzimidazolylbenzimidazole with bromomethylcyanobiphenyl followed by hydrolysis)
RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



IT **114772-54-2**, 4-Bromomethyl-2'-cyanobiphenyl **152628-02-9**,
2-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Telmisartan by reaction of propyldimethylbenzimidazolylbenzimidazole with bromomethylcyanobiphenyl followed by hydrolysis)
RN 114772-54-2 HCAPLUS
CN [1,1'-Biphenyl]-2-carbonitrile, 4'-(bromomethyl)- (9CI) (CA INDEX NAME)



RN 152628-02-9 HCAPLUS
CN 2,5'-Bi-1H-benzimidazole, 1,7'-dimethyl-2'-propyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

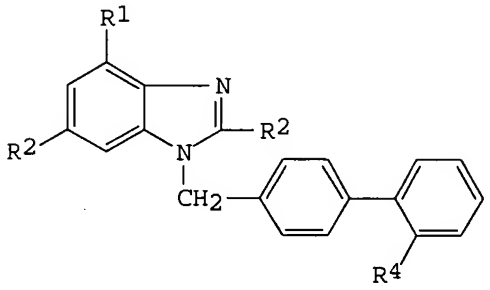
L12 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:560285 HCAPLUS
DOCUMENT NUMBER: 119:160285
TITLE: Benziimidazoles, pharmaceuticals containing them and process for their preparation
INVENTOR(S): Hauel, Norbert; Narr, Berthold; Riess, Uwe; Van Meel,

Jacques; Wienen, Wolfgang; Entzeroth, Michael
PATENT ASSIGNEE(S): Thomae, Dr. Karl, G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

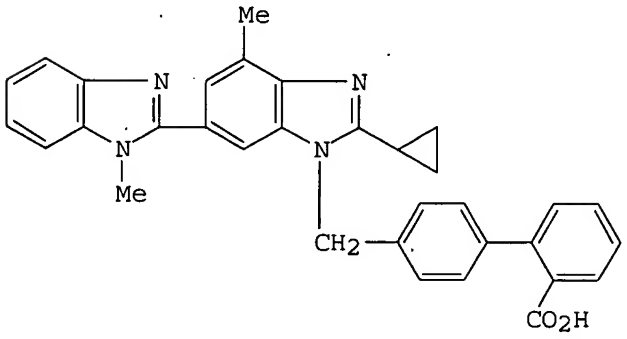
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 543263 | A2 | 19930526 | EP 1992-119261 | 19921111 |
| EP 543263 | A3 | 19930825 | | |
| R: ES | | | | |
| DE 4137812 | A1 | 19930519 | DE 1991-4137812 | 19911116 |
| CZ 287607 | B6 | 20010117 | CZ 1992-306 | 19920204 |
| HR 940752 | B1 | 20010228 | HR 1994-940752 | 19941025 |

PRIORITY APPLN. INFO.: DE 1991-4137812 A 19911116
YU 1992-98 A 19920130
DE 1991-4103492 A 19910206
DE 1991-4117121 A 19910525
CS 1992-306 A 19920204

OTHER SOURCE(S): MARPAT 119:160285
GI




I



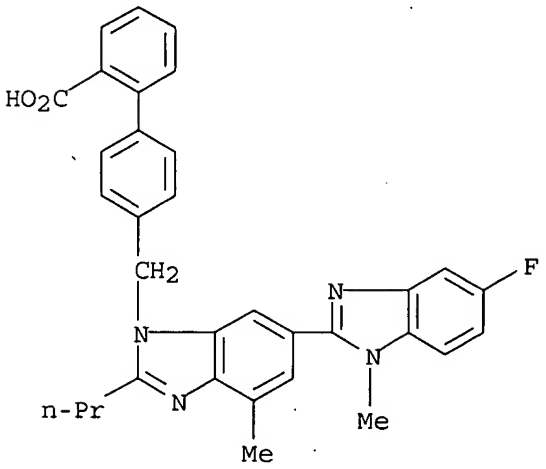

II

AB The title compds., 1-[(1,1'-biphenyl-4-yl)methyl]-1H-benzimidazoles I (R1 = Me, Cl; R2 = heteroaryl; R3 = alkyl, etc; R4 = carboxy, tetrazolyl) and their uses as angiotensin II antagonists are claimed. Condensation of 2-cyclopropyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazole with tert-Bu 4'-(bromomethyl)-1,1'-biphenyl2-carboxylate followed by saponification

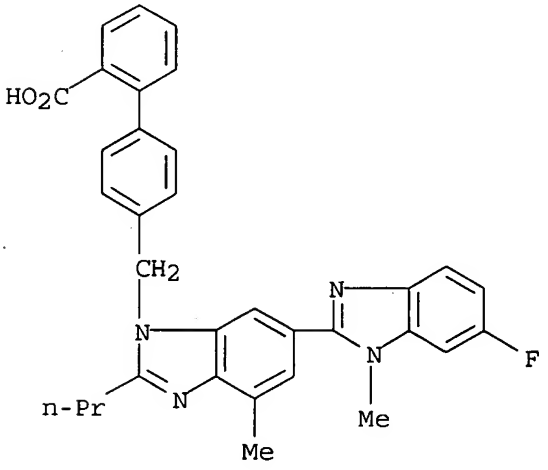
gave 4'-[[2-cyclopropyl-4-methyl-6-(1-methyl-2-benzimidazolyl)]methyl]-1,1'-biphenyl-2-carboxylic acid (II). The angiotensin II-inhibiting IC50 for II was 12 μM.

IT **144702-00-1P 144702-04-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antihypertensive (angiotensin II antagonist))

RN 144702-00-1 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(5-fluoro-1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)

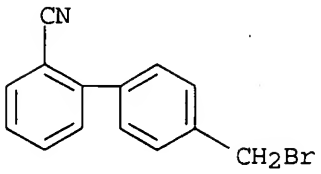



RN 144702-04-5 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(6-fluoro-1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



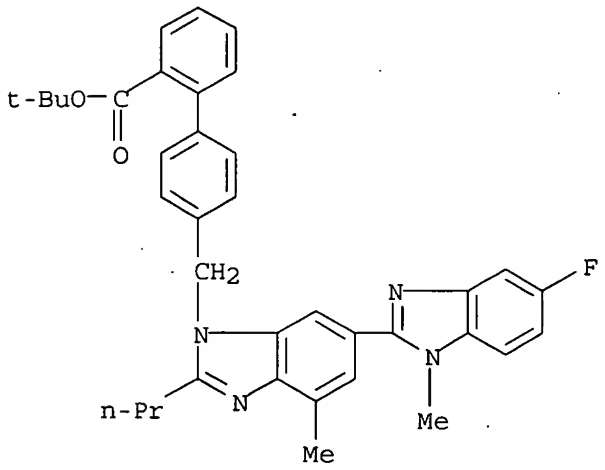

IT **114772-54-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant for [(benzimidazolyl)methyl]biphenyl (antihpertensive angiotensin II antagonist))

RN 114772-54-2 HCAPLUS
CN [1,1'-Biphenyl]-2-carbonitrile, 4'-(bromomethyl)- (9CI) (CA INDEX NAME)

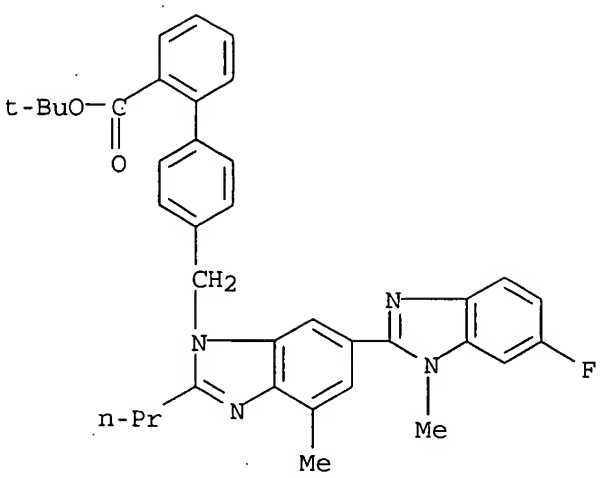



IT **144702-76-1 144702-80-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant for [(benzimidazolyl)methyl]biphenylcarboxylic acid (antihpertensive angiotensin II antagonist))

RN 144702-76-1 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(5-fluoro-1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)




RN 144702-80-7 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(6-fluoro-1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



=> d l15 ibib abs hitstr tot

L15 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1033182 HCAPLUS
TITLE: Therapeutic interchange standardization for angiotensin II receptor antagonists in the treatment of hypertension in the hospital setting
AUTHOR(S): Oltra, B. Porta; Almenar, C. Borras; Torres, N. V. Jimenez
CORPORATE SOURCE: Servicio de Farmacia, Hospital Universitario Dr. Peset, Valencia, Spain
SOURCE: Farmacia Hospitalaria (2005), 29(2), 104-112
CODEN: FAHOE2; ISSN: 1130-6343
PUBLISHER: ARAN Ediciones, S. A.
DOCUMENT TYPE: Journal
LANGUAGE: Spanish
AB Introduction: Standardization of the therapeutic interchange **process** in the hospital setting by the establishment and spreading of standard criteria has been defined as an activity conducent to increased health care quality, and hence improved patient care. Objective: To establish standardized therapeutic swapping for angiotensin II receptor antagonists (ARA-II) in the treatment of blood hypertension, and to evaluate the suitability of therapeutic interchange in an integrated individualized drug dispensation system. Material and methods: Standardized therapeutic interchange was performed based on therapeutic equivalence criteria for ARA-IIs such as candesartan, eprosartan, irbesartan, losartan, olmesartan, **telmisartan**, and valsartan, according to the pharmacodynamic characteristics, dosage recommendations, pharmacokinetic characteristics and interactions of each one of them. The suitability of therapeutic interchange was assessed in terms of standardization or adaptation to this practice developed by using percentage adherence in the previous 12 mo (period A) and during the 12 mo following its implementation and spread (period B).
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:983611 HCAPLUS

DOCUMENT NUMBER: 143:292527
TITLE: Bioavailability and improved delivery of alkaline pharmaceutical drugs
INVENTOR(S): Yu, Ruey J.; Van Scott, Eugene J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 792,273.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2005196418 | A1 | 20050908 | US 2005-50434 | 20050204 |
| US 2004214215 | A1 | 20041028 | US 2004-792273 | 20040304 |
| PRIORITY APPLN. INFO.: | | | US 2004-792273 | A2 20040304 |
| | | | US 2003-452557P | P 20030307 |

AB Embodiments of the invention relate to a composition, a **process** of making the composition, and to the use of the composition The compns. include a mol. complex formed between an alkaline pharmaceutical drug and at least one selected from a hydroxy acid, a polyhydroxy acid, a related acid, a lactone, or combinations thereof. The compns. provide improved bioavailability and improved delivery of the drug into the cutaneous tissues. For example, diphenhydramine hydrochloride 29 g (0.1 mol) was dissolved in water and 5 N sodium hydroxide generating diphenhydramine free base. Gluconolactone 18 g (0.1 mol) was added to form a mol. complex of 0.1 mol diphenhydramine free base with 0.1 mol gluconic acid/gluconolactone. The solution thus obtained was used for various forms of topical formulations including oil-in-water creams, lotions, gels and solns.

L15 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:409366 HCAPLUS
DOCUMENT NUMBER: 142:469377
TITLE: Method for coating implants with active substances by printing
INVENTOR(S): Kunstmann, Juergen; Mayer, Bernhard; Rathenow, Joerg; Asgari, Soheil
PATENT ASSIGNEE(S): Blue Membranes G.m.b.H., Germany
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005042045 | A1 | 20050512 | WO 2004-EP12442 | 20041103 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, | | | | |

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10351150 A1 20050525 DE 2003-10351150 20031103
PRIORITY APPLN. INFO.: DE 2003-10351150 A 20031103

AB The invention relates to a method and a device for applying a defined amount of a coating material to the surface of an implant by way of a printing method, especially using a printing roller. The invention also relates to the use of a printing method, especially of a printing roller for applying a defined amount of a coating material to the surface of an implant to be coated, and to coated implants produced by this method. Metal, metal alloy, ceramic, glass fiber, ceramic, etc. implants are coated by various printing technique. Coating materials are solns., suspensions, emulsions containing active substances or their precursors.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:323779 HCAPLUS
DOCUMENT NUMBER: 142:397824
TITLE: Biocompatibly coated medical implants
INVENTOR(S): Rathenow, Jorg; Ban, Andreas; Kunstmann, Jurgen; Mayer, Bernhard; Asgari, Soheil
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of Appl. No. PCT/EP04/04985.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2005079200 | A1 | 20050414 | US 2004-938995 | 20040910 |
| DE 10322182 | A1 | 20041202 | DE 2003-10322182 | 20030516 |
| DE 10324415 | A1 | 20041216 | DE 2003-10324415 | 20030528 |
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| WO 2004101017 | A2 | 20041125 | WO 2004-EP4985 | 20040510 |
| WO 2004101017 | A3 | 20050303 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
DE 2003-10322182 A 20030516
DE 2003-10324415 A 20030528
DE 2003-10333098 A 20030721
WO 2004-EP4985 A2 20040510

AB Implantable medical devices with biocompatible coatings and **processes** for their production are described. The present invention

relates in particular to medical implantable devices coated with a carbon-containing layer which devices are produced by at least partially coating the device with a polymer film and heating the polymer film in an atmospheric which is essentially free from oxygen to temps. in the region of 200 °C to 2500 °C., a carbon-containing layer being produced on the implantable medical device. Duroplan glass fibers were coated by immersion coating with a com. packaging varnish in an application weight of 2.0x10-4 g/cm2. Following subsequent pyrolysis with carbonization at 800° C. for 48 h, a loss of weight of the coating to 0.33x10-4 g/cm2 took place. The previously colorless coating turned a glossy black and was hardly transparent any longer after carbonization. A test of the adhesion of the coating by bending in a radius of 180° did not result in any detachment, i.e. optically detectable damage to the surface.

L15 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:318166 HCAPLUS
DOCUMENT NUMBER: 143:52909
TITLE: Prediction of intestinal epithelial transport of drug in (Caco-2) cell culture from molecular structure using in silico approaches during early drug discovery
AUTHOR(S): Ponce, Yovani Marrero; Perez, Miguel A. Cabrera; Zaldivar, Vicente Romero; Sanz, Marival Bermejo; Mota, Dany Siverio; Torrens, Francisco
CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical-Pharmacy, Central University of Las Villas, Villa Clara, 54830, Cuba
SOURCE: Internet Electronic Journal of Molecular Design (2005), 4(2), 124-150
CODEN: IEJMAT; ISSN: 1538-6414
URL: ftp://biochempress.com/iejmd_2005_4_0124-pdf
PUBLISHER: BioChem Press
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Motivation: The high interest in the prediction of the intestinal absorption for new chemical entities is generated by the increasing rate in the synthesis of compds. by combinatorial chemical and the extensive cost of the traditional evaluation methods. Method: Novel mol. descriptors have been applied to estimate the intestinal epithelial transport of drug in Caco-2 cell culture. Total and local (atom and atom-type) quadratic indexes used in this study were calculated by TOMOCOMD-CARDD software. Linear Discriminant Anal. (LDA) was used to obtain a quant. model that discriminates the high absorption compds. (P ≥ 8+10-6 cm/s) from those with moderate-poor absorption (P < 8+10-6 cm/s). A data set of 134 diverse structure drugs and two series of drugs-like compds. (12 compds.) were used as training and test set, resp. In addition, Multiple Linear Regression (MLR) has been carried out to derive QSPerR models. All statistical analyses were performed with the STATISTICA software package. Results: The obtained LDA model classified correctly 81.13% of compds. with moderate-poor absorption properties and the 96.30% of compds. with high absorption, showing a global good classification of 90.30% in the training set. The model showed a high Matthews' correlation coefficient (MCC = 0.80). Internal and external validation **processes** to demonstrate the robustness and predictive power of the obtained model were carried out. In this sense, the model classified correctly 87.31% (MCC = 0.73) in the leave-one-out cross-validation procedure. The discriminant model was also assessed by a 10 fold full cross-validation (removing approx. 13 compds. in each cycle, 85.82% of good classification), yielding a MCC of 0.70. Also this model shown an 87.5, 85.6, 84.7, 85.0, 85.3,

83.5, 84.1, 86.2, 85.9 and 85.9% of global good classification when n varied from 2 to 11 in the leave-n-out cross validation procedure. The model was stabilized around 85.9% when n was > 9. In addition, a data set of 7 HIV protease inhibitors (4 linear peptidomimetic and 3 new cyclic urea) and 5 new 6 fluoroquinolones derivs. was used as external test set. The LDA-QSPerR model achieved a MCC of 0.71 (83.33% correct prediction) in this study. This approach permits us to obtain a good explanation of the experiment based on the mol. structural features, evidencing the main role of H-bonding and size properties in permeability **process.** Finally, the model developed was used in the virtual screening of 241 drugs with the percentage of human intestinal absorption (Abs %) values reported. A relationship between the predicted permeability coeffs. in Caco-2 and the Abs % (145 compds. with good data quality) was established, with a percentage of good relation greater than 82 %. A comparison with results derived from other three theor. studies shown a quite satisfactory behavior of the present method. Conclusions: All these results shown that total and local (atom and atom-type) quadratic indexes can successfully predict intestinal permeability and suggest that the proposed methodol. will be a good tool for studying the oral absorption of drug candidates during the drug development **process.**

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:119884 HCAPLUS
DOCUMENT NUMBER: 142:204864
TITLE: Medical implants coated with porous carbon surfaces carrying drugs
INVENTOR(S): Rathenow, Joerg; Asgari, Soheil; Ban, Andreas
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Offen., 15 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 10333099 | A1 | 20050210 | DE 2003-10333099 | 20030721 |
| DE 202004009061 | U1 | 20040916 | DE 2004-202004009061 | 20040528 |
| WO 2004105826 | A2 | 20041209 | WO 2004-EP5785 | 20040528 |
| WO 2004105826 | A3 | 20050623 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

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| US 2005079201 | A1 | 20050414 | US 2004-939021 | 20040910 |

PRIORITY APPLN. INFO.:

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|---|---|
| DE 2003-10324415 | A1 20030528 |
| DE 2003-10333098 | A1 20030721 |
| DE 2003-10333099 | A1 20030721 |
| WO 2004-EP5785 | A2 20040528 |

AB The invention concerns a method for the preparation of medical implants with functionalized surfaces involving the steps: (a)preparation of medical implant that is at least partially coated with a carbon-containing layer; (b) activation of the carbon-containing layer by forming a pores on the surface; (c) functionalization of the activated, carbon-containing surface. The carbon-containing layer is composed of pyrolytically prepared carbon, carbon deposited by CVD or PVD **process**, sputtered carbon, metal carbides, metal carbonitrides, metal oxynitrides, metal oxycarbides or their combinations. The carbon-containing layers are activated by oxidation with air, oxygen, dinitrogen oxide, and oxidizing acids, also at elevated temperature A reduction **process** can also be used for activation. Activated surfaces are functionalized by loading one or more drugs, microorganisms or cells onto the surface. Activated surfaces can be sealed in a CVD or CVI (chemical vapor infiltration) **process.** The implants are prepared from carbon, carbon fibers, ceramics, glass, metals, alloys, artificial bone, stone, minerals. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, bone and joint prosthesis, artificial heart, heart valves, s.c., and i.m. implants can be activated and functionalized.

L15 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:119883 HCAPLUS
DOCUMENT NUMBER: 142:204863
TITLE: Biocompatible coated medical implants with a carbon layer and method for preparation
INVENTOR(S): Rathenow, Joerg; Asgari, Soheil; Ban, Andreas
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Offen., 23 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| DE 202004009060 | U1 | 20040916 | DE 2004-202004009060 | 20040510 |
| WO 2004101017 | A2 | 20041125 | WO 2004-EP4985 | 20040510 |
| WO 2004101017 | A3 | 20050303 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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| DE 202004009061 | U1 | 20040916 | DE 2004-202004009061 | 20040528 |
| WO 2004105826 | A2 | 20041209 | WO 2004-EP5785 | 20040528 |
| WO 2004105826 | A3 | 20050623 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

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|---|---|---|---|---|
| US 2005079200 | A1 | 20050414 | US 2004-938995 | 20040910 |
| US 2005079201 | A1 | 20050414 | US 2004-939021 | 20040910 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10322182 | A1 20030516 |
| | | | DE 2003-10324415 | A1 20030528 |
| | | | DE 2003-10333098 | A1 20030721 |
| | | | DE 2003-10333099 | A1 20030721 |
| | | | WO 2004-EP4985 | A2 20040510 |
| | | | WO 2004-EP5785 | A2 20040528 |

AB The invention concerns a method for the preparation of biocompatible coatings for implants, and medical goods composing the steps (a) coating the medical good at least partially with a polymer film using a coating **process**; (b) heating the polymer film in an oxygen-free atmospheric at 200-2500 °C to obtain a carbon layer on the medical good. The medical goods are heat resistant; they are prepared from carbon, carbon fibers, ceramics, glass, metals, alloys, artificial bone, stone, minerals; during heating they are transferred to their thermostable state. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, bone and joint prosthesis, artificial heart, heart valves, s.c., and i.m. implants can be coated. Other coating methods, e.g. dipping, spraying, printing can be applied. Several carbon layers with various porosity can be formed; biocompatible, biodegradable, non-biodegradable polymer layers can be placed on top of the carbon layers; drugs can be adsorbed onto the layers.

L15 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:965058 HCAPLUS
DOCUMENT NUMBER: 141:415987
TITLE: Preparation of **telmisartan** sodium salt for use in pharmaceutical formulations
INVENTOR(S): Kohlrausch, Anja
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004096215 | A1 | 20041111 | WO 2004-EP4425 | 20040427 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,

SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| DE 10319450 | A1 | 20041118 | DE 2003-10319450 | 20030430 |
| US 2005004107 | A1 | 20050106 | US 2004-825580 | 20040415 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10319450 | A 20030430 |
| | | | US 2003-471675P | P 20030519 |

AB The invention relates to a medicament formulation of the crystalline sodium salt of 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid (**Telmisartan**) and methods for production thereof. **Telmisartan** sodium salt can also be formulated in combination with a diuretics, preferably hydrochlorothiazide. Thus two synthesis of crystalline **telmisartan** sodium salt hemihydrate are described; the first one involves the reaction of **telmisartan** with sodium hydroxide in ethanol-containing toluene, followed by distillation of the solvent and crystallization In the second **process** first **telmisartan** hydrochloride is prepared from 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid tert. Bu ester; the product is then reacted with sodium methylate in toluene that also contains traces of water, isopropanol and methanol. Crystallization again is achieved by the azeotropic distillation of the solvents. A tablet contained (mg): **telmisartan** sodium salt 83.417; mannitol 299.083; microcryst. cellulose 100.000; croscarmellose sodium salt 10.000; magnesium stearate 7.500.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

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|---|---|
| ACCESSION NUMBER: | 2004:759835 HCAPLUS |
| DOCUMENT NUMBER: | 141:277616 |
| TITLE: | Preparation of 3-(1-[3-(1,3-benzothiazol-6-yl)propylcarbamoyl]cycloalkyl)propanoic acid derivatives as nep inhibitors |
| INVENTOR(S): | Hepworth, David |
| PATENT ASSIGNEE(S): | Pfizer Inc., UK |
| SOURCE: | U.S. Pat. Appl. Publ., 27 pp., which CODEN: USXXCO |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | English |
| FAMILY ACC. NUM. COUNT: | 1 |

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004180941 | A1 | 20040916 | US 2004-800065 | 20040312 |
| WO 2004080985 | A1 | 20040923 | WO 2004-IB822 | 20040309 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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| NL 1025709 | A1 | 20040916 | NL 2004-1025709 | 20040312 |
| NL 1025709 | C2 | 20050314 | | |

PRIORITY APPLN. INFO.:

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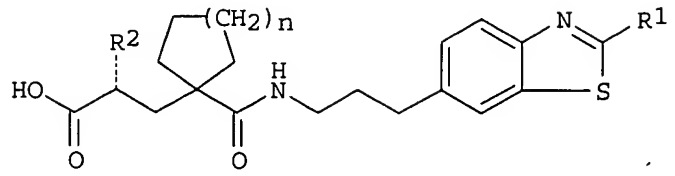
|---|---|---|
| GB 2003-5916 | A | 20030314 |
| US 2003-464608P | P | 20030422 |
| GB 2003-29143 | A | 20031216 |
| US 2004-538079P | P | 20040120 |

OTHER SOURCE(S): MARPAT 141:277616

GI



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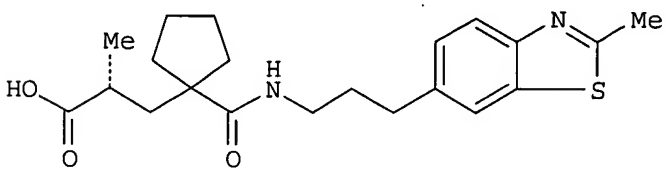

II

AB The invention relates to the use of title compds. I [R1 = H or Me; R2 = Me or Et; n = 1 or 2] as inhibitors of neutral endopeptidase enzyme (NEP), **processes** for the preparation thereof, intermediates used in the preparation thereof and compns. containing said inhibitors. Thus, e.g., II was prepared by amidation of 1-[(2R)-3-tert-butoxy-2-methyl-3-oxopropyl]cyclopentane carboxylic acid with 3-(2-methyl-1,3-benzothiazol-6-yl)propylamine dihydrochloride (preparation given) with subsequent hydrolysis to provide the free acid. I have been demonstrated to possess IC50 values of <20 nanomolar in tests for NEP inhibition and demonstrate a selectivity over soluble secreted endopeptidase (SEP) of at least 1000 fold. These inhibitors have utility in a variety of therapeutic areas including the treatment of male and female sexual dysfunction, particularly female sexual dysfunction (FSD), especially wherein the FSD is female sexual arousal disorder (FSAD).

L15 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:756044 HCAPLUS

DOCUMENT NUMBER: 141:266048

TITLE: Medical implants with carbon-containing surfaces that are functionalized

PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany

SOURCE: Ger. Gebrauchsmusterschrift, 18 pp.
CODEN: GGXXFR

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 202004009061 | U1 | 20040916 | DE 2004-202004009061 | 20040528 |
| DE 10324415 | A1 | 20041216 | DE 2003-10324415 | 20030528 |
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |

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| DE 10333099 | A1 | 20050210 | DE 2003-10333099 | 20030721 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10324415 | A1 20030528 |
| | | | DE 2003-10333098 | A1 20030721 |
| | | | DE 2003-10333099 | A1 20030721 |

AB The invention concerns medical implants with carbon-containing surfaces that are functionalized; the surfaces are prepared by (a) preparing a medical implant with a carbon-containing surface; (b) activation of the carbon layer by creating porosity; (c) functionalization of the activated, carbon-containing layer. The carbon layer can be prepared by pyrolysis, CVD, PVD, sputtering, ion implantation. The medical devices are prepared from carbon, carbon-composite material, glass, ceramics, glass fibers, carbon fibers, metals, stainless steel, titanium, tantalum, platinum, nitinol, alloys, artificial bone, minerals, and their combinations. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, artificial hearts and heart valves, artificial bones and joints are prepared The carbon layer is activated with oxidation or reducing agents in the presence of air, oxygen, nitrogen monoxide, oxidative acids; heat and/or ultrasound can be applied. The activated implant surfaces are functionalized with drugs, microorganisms, plant, animal or human cells. The invention also concerns controlled-release implanted drug delivery systems.

L15 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:756043 HCAPLUS
DOCUMENT NUMBER: 141:266047
TITLE: Medical implants coated with biocompatible carbon-containing layers
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Gebrauchsmusterschrift, 23 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 202004009060 | U1 | 20040916 | DE 2004-202004009060 | 20040510 |
| DE 10322182 | A1 | 20041202 | DE 2003-10322182 | 20030516 |
| DE 10324415 | A1 | 20041216 | DE 2003-10324415 | 20030528 |
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10322182 | A1 20030516 |
| | | | DE 2003-10324415 | A1 20030528 |
| | | | DE 2003-10333098 | A1 20030721 |

AB The invention concerns medical implants that are coated with biocompatible carbon-layers composed; the layers are prepared by (a) at least partial covering or coating of a medical implant with a polymer film; (b) heating the polymer film to 2000-2500°C in an oxygen-free atmospheric The medical device is prepared from carbon, carbon-composite material, glass, ceramics, glass fibers, carbon fibers, metals, stainless steel, titanium, tantalum, platinum, nitinol, alloys, artificial bone, minerals, and their combinations; during heat treatment they are transferred in their heat-stable modifications. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, artificial hearts and heart valves, artificial bones and joints are prepared Polymers are applied by conventional coating techniques, e.g. from polymer solns.; carbon and silicon can be deposited in a PVD or CVD **process.** The biocompatible carbon layer can be coated with a bioresorbant or biodegradable polymer layer, e.g. polylactide. The implants can be loaded

with drugs, microorganisms or cells.

L15 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:719056 HCAPLUS
DOCUMENT NUMBER: 142:85836
TITLE: A new topological descriptors based model for predicting intestinal epithelial transport of drugs in Caco-2 cell culture
AUTHOR(S): Ponce, Yovani Marrero; Perez, Miguel A. Cabrera; Zaldivar, Vicente Romero; Diaz, Humberto Gonzalez; Torrens, Francisco
CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical-Pharmacy, Central University of Las Villas, Santa Clara, 54830, Cuba
SOURCE: Journal of Pharmacy & Pharmaceutical Sciences (2004), 7(2), 186-199
CODEN: JPPSFY; ISSN: 1482-1826
URL: http://www.ualberta.ca/~csps/JPPS7(2)/Y.Ponce/caco-2.pdf
PUBLISHER: Canadian Society for Pharmaceutical Sciences
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Purpose: Quant. Structure-Permeability Relationships (QSPerR) of the intestinal permeability across the (Caco-2) cells monolayer could be obtained by the application of new mol. descriptors. Method: A novel topol.-mol. approach to computer mol. design (TOMOCOMD-CARDD) has been used to estimate the intestinal-epithelial transport of drug in Caco-2 cell culture. Results: The Permeability Coeffs. in Caco-2 cells (P) for 33 structurally diverse drugs were well described using quadratic indexes of the mol. pseudograph's atom adjacency matrix as mol. descriptors. A quant. model that discriminates the high-absorption compds. from those with moderate-poor absorption was obtained for the training data set, showing a global classification of 87.87%. In addition, two QSPerR models, through a multiple linear regression, were obtained to predict the P [apical to basolateral (AP-BL) and basolateral to apical (BL-AP)]. A leave-n-out and leave-one-out cross-validation procedure revealed that the discriminant and regression models resp., had a good predictability. Furthermore, others 18 drugs were selected as a test set in order to assess. the predictive power of the models and the accuracy of the final prediction was similar to achieve for the data set. Besides, the use of both regression models, in a combinative way, is possible to predict the Permeability Directional Ratio (PDR, BL→AP/AP→BL) value.
The found models were used in virtual screening of drug intestinal permeability and a relationship between calculated P and percentage of human intestinal absorption for several compds. was established. Furthermore, this approximation permits us to obtain a good explanation of the experiment based
on the mol. structural features. Conclusions: These results suggest that the proposed method is able to predict the P values and it proved to be a good tool for studying the oral absorption of drug candidates during the drug development **process.**
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:528419 HCAPLUS
DOCUMENT NUMBER: 141:218304
TITLE: ADME Evaluation in Drug Discovery. 5. Correlation of Caco-2 Permeation with Simple Molecular Properties

AUTHOR(S): Hou, T. J.; Zhang, W.; Xia, K.; Qiao, X. B.; Xu, X. J.
CORPORATE SOURCE: College of Chemistry and Molecular Engineering, Peking University, Beijing, 100871, Peop. Rep. China
SOURCE: Journal of Chemical Information and Computer Sciences (2004), 44(5), 1585-1600
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The correlations between Caco-2 permeability (logPapp) and mol. properties have been investigated. A training set of 77 structurally diverse organic mols. was used to construct significant QSAR models for Caco-2 cell permeation. Cellular permeation was found to depend primarily upon exptl. distribution coefficient (logD) at pH = 7.4, high charged polar surface area (HCPSA), and radius of gyration (rgyr). Among these three descriptors, logD may have the largest impact on diffusion through Caco-2 cell because logD shows obvious linear correlation with logPapp (r=0.703) when logD is smaller than 2.0. High polar surface area will be unfavorable to achieve good Caco-2 permeability because higher polar surface area will introduce stronger H-bonding interactions between Caco-2 cells and drugs. The comparison among HCPSA, PSA (polar surface area), and TPSA (topol. polar surface area) implies that high-charged atoms may be more important to the interactions between Caco-2 cell and drugs. Besides logD and HCPSA, rgyr is also closely connected with Caco-2 permeabilities. The mols. with larger rgyr are more difficult to cross Caco-2 monolayers than those with smaller rgyr. The descriptors included in the prediction models permit the interpretation in structural terms of the passive permeability **process**, evidencing the main role of lipoliphilicity, H-bonding, and bulk properties. Besides these three mol. descriptors, the influence of other mol. descriptors was also investigated. From the calculated results, it can be found that introducing descriptors concerned with mol. flexibility can improve the linear correlation. The resulting model with four descriptors bears good statistical significance, n = 77, r = 0.82, q = 0.79, s = 0.45, F = 35.7. The actual predictive abilities of the QSAR model were validated through an external validation test set of 23 diverse compds. The predictions for the tested compds. are as the same accuracy as the compds. of the training set and significantly better than those predicted by using the model reported. The good predictive ability suggests that the proposed model may be a good tool for fast screening of logPapp for compound libraries or large sets of new chemical entities via combinatorial chemical synthesis.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:189973 HCAPLUS
DOCUMENT NUMBER: 141:235641
TITLE: Total and local quadratic indices of the "molecular pseudograph's atom adjacency matrix". Application to prediction of Caco-2 permeability of drugs
AUTHOR(S): Ponce, Yovani Marrero; Perez, Miguel Angel Cabrera; Zaldivar, Vicente Romero; Ofori, Ernest; Montero, Luis A.
CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical-Pharmacy, Central University of Las Villas, Villa Clara, 54830, Cuba
SOURCE: International Journal of Molecular Sciences (2003), 4(8/9), 512-536
CODEN: IJMCFK; ISSN: 1422-0067

URL: http://www.mdpi.org/ijms/papers/i4080512.pdf
PUBLISHER: Molecular Diversity Preservation International
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The high interest in the prediction of the intestinal absorption for New Chemical Entities (NCEs) is generated by the increasing rate in the synthesis of compds. by combinatorial chemical and the extensive cost of the traditional evaluation methods. Quant. Structure-Permeability Relationships (QSPerR) of the intestinal permeability across the Caco-2 cells monolayer (PCaco-2) could be obtained by the application of new mol. descriptors. In this sense, quadratic indexes of the "mol. pseudograph's atom adjacency matrix" and multiple linear regression anal. were used to obtain good quant. models to determine the PCaco-2. QSPerR models found are significant from a statistical point of view. The total and local quadratic indexes were calculated with the TOMO-COMD software. A leave-one-out cross-validation procedure (internal validation) and the evaluation of external test set of 20 drugs (external validation) revealed that regression models had a good predictive power. A comparison with results derived from other theor. studies shown a quite satisfactory behavior of the present method. The descriptors included in the prediction models permitted the interpretation in structural terms of the permeability **process**, evidencing the main role of H-bonding and size properties. The models found were used in virtual screening of drug intestinal permeability and a relationship between PCaco-2 calculated and percentage of human intestinal absorption for the 72 compds. was established. These results suggest that the proposed method is able to predict PCaco-2, being a good tool for screening of Pcaco-2 for large sets of NCEs synthesized via combinatorial chemical approach.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:99589 HCAPLUS
DOCUMENT NUMBER: 140:309530
TITLE: Prediction of MS/MS Data. 1. a focus on pharmaceuticals containing carboxylic acids
AUTHOR(S): Bandu, Mary L.; Watkins, Kathryn R.; Bretthauer, Melinda L.; Moore, Christopher A.; Desaire, Heather
CORPORATE SOURCE: Department of Chemistry, University of Kansas, Lawrence, KS, 66045, USA
SOURCE: Analytical Chemistry (2004), 76(6), 1746-1753
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Metabolite identification is a necessary step in developing safe and effective drugs. Metabolite anal. typically involves rapid identification of the chemical composition of the metabolite by automated HPLC-MS methods, followed by the laborious **process** of identifying the structure of the metabolite. Since MS is typically utilized to identify the metabolite, it is logical to utilize MS/MS to structurally characterize the sample. However, interpretation of MS/MS data may not provide sufficient information, as fragmentation pathways are not well understood or predictable. Therefore, other more time-consuming methods of anal. are often undertaken. If the dissociation rules for low-energy MS/MS expts. were clearly defined for all classes of compds., more information would be obtained from MS/MS data, and metabolite identification would proceed more rapidly. We are currently developing methods to define these fragmentation rules. By screening .apprx.100 carboxylic acids at a time

and applying knowledge of phys.-organic chemical, predictive rules are under development that describe how compds. dissociate under low-energy collision-induced dissociation conditions. Studies of carboxylic acid dissociation demonstrate that this approach is practical and reliable. Dissociation rules were predicted with a 90% success rate, when tested on acid-containing pharmaceuticals. This predictive power cannot be matched by any com. available software. This study, and others like it, will be used to develop algorithms that more rapidly identify drug metabolites and degradation products, based on MS/MS data. Such algorithms will benefit drug development for all types of pharmaceuticals.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:759933 HCAPLUS
DOCUMENT NUMBER: 139:301175
TITLE: PROGRESS beyond HOPE and LIFE: the ONTARGET trial programme
AUTHOR(S): Sleight, P.
CORPORATE SOURCE: John Radcliffe Hospital, Oxford, UK
SOURCE: European Heart Journal Supplements (2003), 5(Suppl. F), F40-F47
CODEN: EHJSFT; ISSN: 1520-765X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Large-scale cardiovascular trials traditionally have targeted clin. hypertension, diabetes or survivors of myocardial infarction, but the recent trend in such trials has been to consider the treatment of high-risk individuals rather than specific diseases. This allows the use of a much broader screening **process** to enroll patients. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) act directly on the renin-angiotensin system to effect blood pressure control. The Heart Outcomes Prevention Evaluation (HOPE) and the Perindopril pROtection against REcurrent Stroke Study (PROGRESS) showed that angiotensin-converting enzyme inhibitors (ramipril and perindopril plus the diuretic indapamide), significantly decreased the risk for stroke and other adverse cardiovascular outcomes. Both studies showed benefits in patients with conventionally normal blood pressure. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial showed that losartan, an ARB, could also significantly decrease the risk of stroke to an extent greater than that predicted by the decrease in blood pressure. The ONgoing **Telmisartan** Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) Trial Program is currently underway to study the effect of ramipril and the ARB **telmisartan**, and a combination of the two agents in patients at high risk of cardiovascular disease.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:700804 HCAPLUS
DOCUMENT NUMBER: 140:28746
TITLE: Synthesis of **telmisartan**
AUTHOR(S): Fu, Yan; Guo, Yi; Yang, Shuang-ge; Chen, Li-li; Yan, Li-xue
CORPORATE SOURCE: Faculty of Medicinal Chemistry, Pharmaceutical Science College, Hebei Medical University, Shijiazhuang, 050017, Peop. Rep. China

SOURCE: Zhongguo Xinyao Zazhi (2003), 12(7), 538-539
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 140:28746

AB The title compound was prepared from 7-methyl-2-propyl-1H-benzimidazole-5-carboxylic acid by cyclocondensation with N-methyl-o-phenylenediamine, alkylation with t-Bu 4'-(bromomethyl)biphenyl-2-carboxylate and hydrolysis. The overall yield was 45.6%. The **process** gives improved yield and decreased cost.

L15 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:754995 HCAPLUS
DOCUMENT NUMBER: 137:268473
TITLE: Porous drug matrices and methods of manufacture thereof
INVENTOR(S): Straub, Julie; Altreuter, David; Bernstein, Howard; Chickering, Donald E.; Khattak, Sarwat; Randall, Greg
PATENT ASSIGNEE(S): Acusphere Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U. S. 6,395,300.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2002142050 | A1 | 20021003 | US 2002-53929 | | 20020122 |
| US 6395300 | B1 | 20020528 | US 1999-433486 | | 19991104 |
| US 6645528 | B1 | 20031111 | US 2000-694407 | | 20001023 |
| US 6922983 | B1 | 20050823 | US 2000-706045 | | 20001103 |
| ZA 2001010347 | A | 20030730 | ZA 2001-10347 | | 20011218 |
| US 2005048116 | A1 | 20050303 | US 2004-924642 | | 20040824 |
| US 2005058710 | A1 | 20050317 | US 2004-928886 | | 20040827 |
| PRIORITY APPLN. INFO.: | | | US 1999-136323P | P | 19990527 |
| | | | US 1999-158659P | P | 19991008 |
| | | | US 1999-433486 | A2 | 19991104 |
| | | | US 2002-53929 | A3 | 20020122 |

AB Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aqueous media. The drug matrixes preferably are made using a **process** that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solution and hydrophilic or hydrophobic excipients that stabilize the drug and inhibit crystallization, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. Hydrophobic or hydrophilic excipients may be selected to stabilize the drug in crystalline form by inhibiting crystal growth or to stabilize the drug in amorphous form by preventing crystallization The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is

used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration. Thus, 5.46 g of PEG 8000, 0.545 g of prednisone, and 0.055 g of Span 40 were dissolved in 182 mL of methylene chloride. A solution of 3.27 g of ammonium bicarbonate in 18.2 mL of water was added to the organic solution (phase ratio 1:10) and homogenized for 5 min at 16,000 RPM.

The resulting emulsion was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas.

L15 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:750331 HCAPLUS
DOCUMENT NUMBER: 139:62535
TITLE: Rate-Limited Steps of Human Oral Absorption and QSAR Studies
AUTHOR(S): Zhao, Yuan H.; Abraham, Michael H.; Le, Joelle; Hersey, Anne; Luscombe, Chris N.; Beck, Gordon; Sherborne, Brad; Cooper, Ian
CORPORATE SOURCE: Department of Chemistry, University College London, London, WC1H 0AJ, UK
SOURCE: Pharmaceutical Research (2002), 19(10), 1446-1457
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose. To classify the dissoln. and diffusion rate-limited drugs and establish quant. relationships between absorption and mol. descriptors. Methods. Absorption consists of kinetic transit **processes** in which dissoln., diffusion, or perfusion **processes** can become the rate-limited step. The absorption data of 238 drugs have been classified into either dissoln. or diffusion rate-limited based on an equilibrium method developed from solubility, dose, and percentage of absorption. A nonlinear absorption model derived from first-order kinetics has been developed to identify the relationship between percentage of drug absorption and mol. descriptors. Results. Regression anal. was performed between percentage of absorption and mol. descriptors. The descriptors used were ClogP, mol. polar surface area, the number of hydrogen-bonding acceptors and donors, and Abraham descriptors. Good relationships were found between absorption and Abraham descriptors or ClogP. Conclusions. The absorption models can predict the following three BCS (Biopharmaceutics Classification Scheme) classes of compds.: class I, high solubility and high permeability; class III, high solubility and low permeability; class IV, low solubility and low permeability.

The absorption models overpredict the absorption of class II, low solubility and high permeability compds. because dissoln. is the rate-limited step of absorption.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:736138 HCAPLUS
DOCUMENT NUMBER: 137:253025
TITLE: **Process** for producing sustained release preparation
INVENTOR(S): Shiraishi, Keiko; Yamagata, Yutaka; Hata, Yoshio

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002074340 | A1 | 20020926 | WO 2002-JP2404 | 20020314 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1369130 | A1 | 20031210 | EP 2002-705171 | 20020314 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003212758 | A2 | 20030730 | JP 2002-72124 | 20020315 |
| US 2004121008 | A1 | 20040624 | US 2003-471736 | 20030915 |
| PRIORITY APPLN. INFO.: | | | JP 2001-77157 A | 20010316 |
| | | | JP 2001-353757 A | 20011119 |
| | | | WO 2002-JP2404 W | 20020314 |

OTHER SOURCE(S): MARPAT 137:253025

AB Disclosed are a **process** for producing a sustained release preparation characterized by comprising removing a solvent from an organic solvent solution containing a hardly water soluble nonpeptidic physiol. active compound, a polyvalent metal compound and a biodegradable polymer in an amount exceeding the solubility of the biodegradable polymeric in the organic solvent in the absence of the polyvalent metal compound; sustained release prepns. obtained by the above production **process**; sustained release solid medicinal compns. containing a nonpeptidic physiol. active substance and a biodegradable polymer, wherein about 0.05% by weight, based on the composition weight, or more of a polyvalent metal is present on the composition surface; etc. In these sustained release prepns., the hardly water-soluble nonpeptidic physiol. active compound is uniformly distributed and the sustained release effect of the hardly water-soluble nonpeptidic physiol. active compound can be stably achieved. Moreover, medicinal compns. containing a nonpeptidic physiol. active substance wherein the early release of the physiol. active substance is efficiently controlled, a **process** for producing the same, etc. are provided. For example, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid 2 g, zinc acetate dihydrate 0.996 g, and polylactic acid 3.67 g were dissolved in dichloromethane/methanol mixture The solution was added to an aqueous solution of polyvinyl alc. to give an O/W emulsion, which was worked up to obtain sustained-release microcapsules.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:617864 HCAPLUS
DOCUMENT NUMBER: 135:185483

TITLE: Sustained-release compositions of physiologically active compounds hardly-soluble in water and production **process** and use of the same
INVENTOR(S): Kamei, Shigeru; Ojima, Mami; Kitayoshi, Takahito; Igari, Yasutaka
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2001060410 | A1 | 20010823 | WO 2001-JP1191 | | 20010220 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | |
| CA 2400845 | AA | 20010823 | CA 2001-2400845 | | 20010220 |
| AU 2001032348 | A5 | 20010827 | AU 2001-32348 | | 20010220 |
| EP 1258254 | A1 | 20021120 | EP 2001-904560 | | 20010220 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | | |
| JP 2001316296 | A2 | 20011113 | JP 2001-44602 | | 20010221 |
| US 2003068374 | A1 | 20030410 | US 2002-204185 | | 20020819 |
| PRIORITY APPLN. INFO.: | | | JP 2000-48980 | A | 20000221 |
| | | | WO 2001-JP1191 | W | 20010220 |

OTHER SOURCE(S): MARPAT 135:185483
AB Disclosed are sustained-release prepns. containing a physiol. active substance hardly soluble in water, a component obtained by treating with water a polyvalent metal compound hardly soluble in water and a biodegradable polymer which are improved in the release-control and stabilization of the physiol. active substance hardly soluble in water and can be produced by a **process** suitable for mass production Sustained-release microcapsules were formulated from candesartan, zinc oxide, glycolic acid-lactic acid copolymer.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:861473 HCAPLUS
DOCUMENT NUMBER: 134:32972
TITLE: Porous drug matrixes containing polymers and sugars and methods of their manufacture
INVENTOR(S): Straub, Julie; Bernstein, Howard; Chickering, Donald E., III; Khatak, Sarwat; Randall, Greg
PATENT ASSIGNEE(S): Acusphere, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000072827 | A2 | 20001207 | WO 2000-US14578 | 20000525 |
| WO 2000072827 | A3 | 20010125 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6395300 | B1 | 20020528 | US 1999-433486 | 19991104 |
| CA 2371836 | AA | 20001207 | CA 2000-2371836 | 20000525 |
| EP 1180020 | A2 | 20020220 | EP 2000-939365 | 20000525 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 2000010984 | A | 20020430 | BR 2000-10984 | 20000525 |
| JP 2003500438 | T2 | 20030107 | JP 2000-620939 | 20000525 |
| NZ 516083 | A | 20030829 | NZ 2000-516083 | 20000525 |
| AU 768022 | B2 | 20031127 | AU 2000-54459 | 20000525 |
| US 2002041896 | A1 | 20020411 | US 2001-798824 | 20010302 |
| US 6610317 | B2 | 20030826 | | |
| NO 2001005753 | A | 20020128 | NO 2001-5753 | 20011126 |
| ZA 2001010347 | A | 20030730 | ZA 2001-10347 | 20011218 |
| PRIORITY APPLN. INFO.: | | | US 1999-136323P P | 19990527 |
| | | | US 1999-158659P P | 19991008 |
| | | | US 1999-433486 A | 19991104 |
| | | | US 2000-186310P P | 20000302 |
| | | | WO 2000-US14578 W | 20000525 |

AB Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aqueous media. The drug matrixes preferably are made using a **process** that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solns., and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration. Paclitaxel or docetaxel can be provided in a porous matrix form, which allows the drug to be formulated without solubilizing agents and administered as a bolus. For example, a nifedipine-loaded organic solution was prepared by dissolving 9.09 g of PEG 3350, 2.27 g of nifedipine, and 0.009 g of lecithin in 182 mL of methylene chloride. An aqueous solution was prepared by dissolving 3.27 g of NH4HCO3 and 0.91 g of PEG 3350 in 1.82 mL

of water. The aqueous and organic solns. were homogenized and resulting emulsion
was spray dried. A suspension of the porous nifedipine drug matrix was prepared in 5% dextrose solution at a concentration of 2.5 mg/mL. A bolus injection
of the suspension was tolerated when administrated to dogs.

L15 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:226459 HCAPLUS
DOCUMENT NUMBER: 132:342771
TITLE: Evaluation of an accelerated Caco-2 cell permeability model
AUTHOR(S): Liang, Earvin; Chessic, Kelli; Yazdanian, Mehran
CORPORATE SOURCE: Pharmaceutics Department, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, 06877, USA
SOURCE: Journal of Pharmaceutical Sciences (2000), 89(3), 336-345
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An accelerated 3-7 day Caco-2 cell permeability model was examined and compared to the traditional 21-25 day model. Caco-2 cell permeability coeffs. (PCaco-2) of 33 structurally diverse small mol. weight compds. from apical to basolateral (AP→BL) direction in the accelerated model were approx. twice those in the traditional model. As observed with microscopy and transepithelial elec. resistance measurements, this difference was attributed to less confluent and differentiated Caco-2 cell monolayers in the accelerated model. However, there were no significant differences in rank ordering of the compds. The expression of P-glycoprotein in the accelerated model was shown to be significantly less than that in the traditional model. This resulted in lower permeability directional ratios defined as the ratio between permeability coeffs. from BL→AP and from AP→BL for compds. that were cellular efflux pump substrates. The accelerated model may not be suitable for studying cellular efflux pumps such as P-glycoproteins. However, it is a feasible alternative to the traditional model for rank ordering of compds. in the **process** of drug discovery and development by significantly improving the turnover time and labor efficiency. This makes it an excellent Caco-2 cell permeability model for high through-put screening.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L17 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:983611 HCAPLUS
DOCUMENT NUMBER: 143:292527
TITLE: Bioavailability and improved delivery of alkaline pharmaceutical drugs
INVENTOR(S): Yu, Ruey J.; Van Scott, Eugene J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 792,273.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

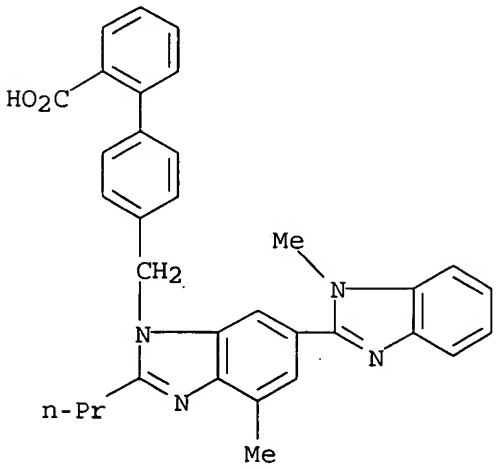
| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2005196418 | A1 | 20050908 | US 2005-50434 | | 20050204 |
| US 2004214215 | A1 | 20041028 | US 2004-792273 | | 20040304 |
| PRIORITY APPLN. INFO.: | | | US 2004-792273 | A2 | 20040304 |
| | | | US 2003-452557P | P | 20030307 |

AB Embodiments of the invention relate to a composition, a **process** of making the composition, and to the use of the composition The compns. include a mol. complex formed between an alkaline pharmaceutical drug and at least one selected from a hydroxy acid, a polyhydroxy acid, a related acid, a lactone, or combinations thereof. The compns. provide improved bioavailability and improved delivery of the drug into the cutaneous tissues. For example, diphenhydramine hydrochloride 29 g (0.1 mol) was dissolved in water and 5 N sodium hydroxide generating diphenhydramine free base. Gluconolactone 18 g (0.1 mol) was added to form a mol. complex of 0.1 mol diphenhydramine free base with 0.1 mol gluconic acid/gluconolactone. The solution thus obtained was used for various forms of topical formulations including oil-in-water creams, lotions, gels and solns.

IT **144701-48-4, Telmisartan**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(bioavailability and improved delivery of alkaline drugs by complexation with acids or lactones)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:409366 HCAPLUS

DOCUMENT NUMBER: 142:469377

TITLE: Method for coating implants with active substances by printing

INVENTOR(S): Kunstmann, Juergen; Mayer, Bernhard; Rathenow, Joerg; Asgari, Soheil

PATENT ASSIGNEE(S): Blue Membranes G.m.b.H., Germany

SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005042045 | A1 | 20050512 | WO 2004-EP12442 | 20041103 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10351150 | A1 | 20050525 | DE 2003-10351150 | 20031103 |

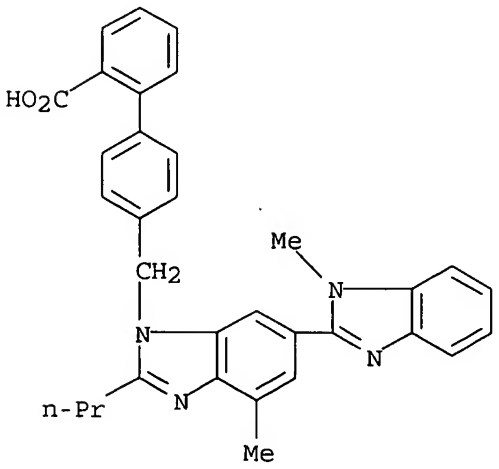
PRIORITY APPLN. INFO.: DE 2003-10351150 A 20031103

AB The invention relates to a method and a device for applying a defined amount of a coating material to the surface of an implant by way of a printing method, especially using a printing roller. The invention also relates to the use of a printing method, especially of a printing roller for applying a defined amount of a coating material to the surface of an implant to be coated, and to coated implants produced by this method. Metal, metal alloy, ceramic, glass fiber, ceramic, etc. implants are coated by various printing technique. Coating materials are solns., suspensions, emulsions containing active substances or their precursors.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for coating implants with active substances by printing)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:323779 HCAPLUS
DOCUMENT NUMBER: 142:397824
TITLE: Biocompatibly coated medical implants
INVENTOR(S): Rathenow, Jorg; Ban, Andreas; Kunstmann, Jurgen; Mayer, Bernhard; Asgari, Soheil
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of Appl. No. PCT/EP04/04985.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2005079200 | A1 | 20050414 | US 2004-938995 | 20040910 |
| DE 10322182 | A1 | 20041202 | DE 2003-10322182 | 20030516 |
| DE 10324415 | A1 | 20041216 | DE 2003-10324415 | 20030528 |
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| WO 2004101017 | A2 | 20041125 | WO 2004-EP4985 | 20040510 |
| WO 2004101017 | A3 | 20050303 | | |

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

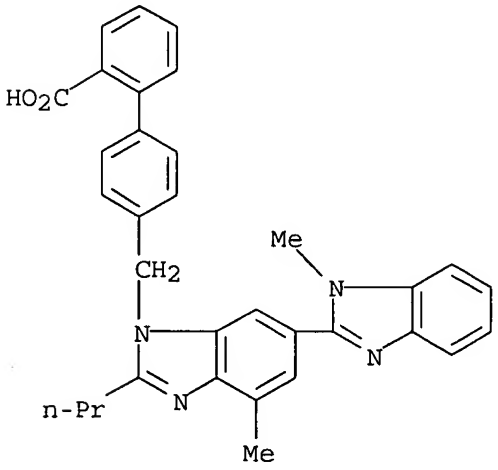
PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 2003-10322182 | A | 20030516 |
| DE 2003-10324415 | A | 20030528 |
| DE 2003-10333098 | A | 20030721 |
| WO 2004-EP4985 | A2 | 20040510 |

AB Implantable medical devices with biocompatible coatings and **processes** for their production are described. The present invention relates in particular to medical implantable devices coated with a carbon-containing layer which devices are produced by at least partially coating the device with a polymer film and heating the polymer film in an atmospheric which is essentially free from oxygen to temps. in the region of 200 °C to 2500 °C., a carbon-containing layer being produced on the implantable medical device. Duroplan glass fibers were coated by immersion coating with a com. packaging varnish in an application weight of 2.0x10-4 g/cm2. Following subsequent pyrolysis with carbonization at 800° C. for 48 h, a loss of weight of the coating to 0.33x10-4 g/cm2 took place. The previously colorless coating turned a glossy black and was hardly transparent any longer after carbonization. A test of the adhesion of the coating by bending in a radius of 180° did not result in any detachment, i.e. optically detectable damage to the surface.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(biocompatibly coated medical implants)
RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



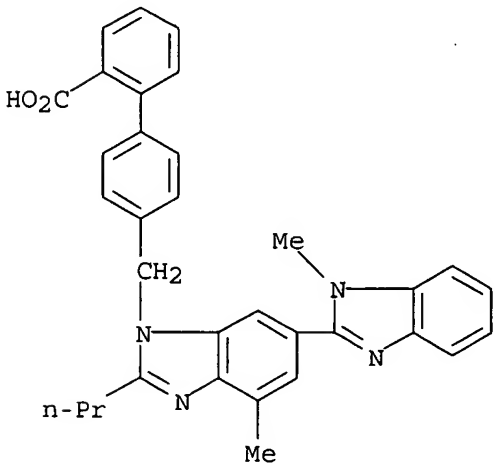

L17 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:318166 HCAPLUS
DOCUMENT NUMBER: 143:52909
TITLE: Prediction of intestinal epithelial transport of drug in (Caco-2) cell culture from molecular structure using in silico approaches during early drug discovery
AUTHOR(S): Ponce, Yovani Marrero; Perez, Miguel A. Cabrera; Zaldivar, Vicente Romero; Sanz, Marival Bermejo; Mota, Dany Siverio; Torrens, Francisco
CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical-Pharmacy, Central University of Las Villas, Villa Clara, 54830, Cuba
SOURCE: Internet Electronic Journal of Molecular Design (2005), 4(2), 124-150
CODEN: IEJMAT; ISSN: 1538-6414
URL: ftp://biochempress.com/iejmd_2005_4_0124.pdf
PUBLISHER: BioChem Press
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Motivation: The high interest in the prediction of the intestinal absorption for new chemical entities is generated by the increasing rate in the synthesis of compds. by combinatorial chemical and the extensive cost of the traditional evaluation methods. Method: Novel mol. descriptors have been applied to estimate the intestinal epithelial transport of drug in Caco-2 cell culture. Total and local (atom and atom-type) quadratic indexes used in this study were calculated by TOMOCOMD-CARDD software. Linear Discriminant Anal. (LDA) was used to obtain a quant. model that discriminates the high absorption compds. ($P \geq 8+10-6$ cm/s) from those with moderate-poor absorption ($P < 8+10-6$ cm/s). A data set of 134 diverse structure drugs and two series of drugs-like compds. (12 compds.) were used as training and test set, resp. In addition, Multiple Linear Regression (MLR) has been carried out to derive QSPerR models. All statistical analyses were performed with the STATISTICA software package. Results: The obtained LDA model classified correctly 81.13% of compds.

with moderate-poor absorption properties and the 96.30% of compds. with high absorption, showing a global good classification of 90.30% in the training set. The model showed a high Matthews' correlation coefficient (MCC = 0.80). Internal and external validation **processes** to demonstrate the robustness and predictive power of the obtained model were carried out. In this sense, the model classified correctly 87.31% (MCC = 0.73) in the leave-one-out cross-validation procedure. The discriminant model was also assessed by a 10 fold full cross-validation (removing approx. 13 compds. in each cycle, 85.82% of good classification), yielding a MCC of 0.70. Also this model shown an 87.5, 85.6, 84.7, 85.0, 85.3, 83.5, 84.1, 86.2, 85.9 and 85.9% of global good classification when n varied from 2 to 11 in the leave-n-out cross validation procedure. The model was stabilized around 85.9% when n was > 9. In addition, a data set of 7 HIV protease inhibitors (4 linear peptidomimetic and 3 new cyclic urea) and 5 new 6 fluoroquinolones derivs. was used as external test set. The LDA-QSPerR model achieved a MCC of 0.71 (83.33% correct prediction) in this study. This approach permits us to obtain a good explanation of the experiment based on the mol. structural features, evidencing the main role of H-bonding and size properties in permeability **process.** Finally, the model developed was used in the virtual screening of 241 drugs with the percentage of human intestinal absorption (Abs %) values reported. A relationship between the predicted permeability coeffs. in Caco-2 and the Abs % (145 compds. with good data quality) was established, with a percentage of good relation greater than 82 %. A comparison with results derived from other three theor. studies shown a quite satisfactory behavior of the present method. Conclusions: All these results shown that total and local (atom and atom-type) quadratic indexes can successfully predict intestinal permeability and suggest that the proposed methodol. will be a good tool for studying the oral absorption of drug candidates during the drug development **process.**

IT **144701-48-4, Telmisartan**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study)
(total and local atom and atom-type quadratic index successfully predict intestinal permeability in human Caco-2 cell suggesting in silico approach is good tool for studying oral absorption of drug candidate during drug development **process**)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:119884 HCAPLUS
DOCUMENT NUMBER: 142:204864
TITLE: Medical implants coated with porous carbon surfaces carrying drugs
INVENTOR(S): Rathenow, Joerg; Asgari, Soheil; Ban, Andreas
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Offen., 15 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 10333099 | A1 | 20050210 | DE 2003-10333099 | 20030721 |
| DE 202004009061 | U1 | 20040916 | DE 2004-202004009061 | 20040528 |
| WO 2004105826 | A2 | 20041209 | WO 2004-EP5785 | 20040528 |
| WO 2004105826 | A3 | 20050623 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
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| US 2005079201 | A1 | 20050414 | US 2004-939021 | 20040910 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 2003-10324415 | A1 | 20030528 |
| DE 2003-10333098 | A1 | 20030721 |
| DE 2003-10333099 | A1 | 20030721 |
| WO 2004-EP5785 | A2 | 20040528 |

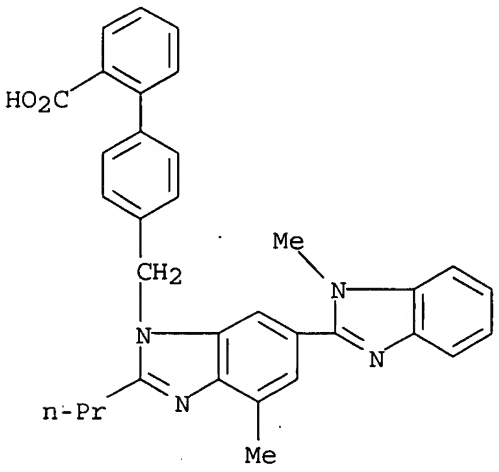
AB The invention concerns a method for the preparation of medical implants with functionalized surfaces involving the steps: (a)preparation of medical implant that is at least partially coated with a carbon-containing layer; (b) activation of the carbon-containing layer by forming a pores on the surface; (c) functionalization of the activated, carbon-containing surface. The carbon-containing layer is composed of pyrolytically prepared carbon, carbon deposited by CVD or PVD **process**, sputtered carbon, metal carbides, metal carbonitrides, metal oxynitrides, metal oxycarbides or their combinations. The carbon-containing layers are activated by oxidation with air, oxygen, dinitrogen oxide, and oxidizing acids, also at elevated temperature A reduction **process** can also be used for activation. Activated surfaces are functionalized by loading one or more drugs, microorganisms or cells onto the surface. Activated surfaces can be sealed in a CVD or CVI (chemical vapor infiltration) **process.** The implants are prepared from carbon, carbon fibers, ceramics, glass, metals, alloys, artificial bone, stone, minerals. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, bone and joint prosthesis,

artificial heart, heart valves, s.c., and i.m. implants can be activated and functionalized.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medical implants coated with porous carbon surfaces carrying drugs)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:119883 HCAPLUS
DOCUMENT NUMBER: 142:204863
TITLE: Biocompatible coated medical implants with a carbon layer and method for preparation
INVENTOR(S): Rathenow, Joerg; Asgari, Soheil; Ban, Andreas
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Offen., 23 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| DE 202004009060 | U1 | 20040916 | DE 2004-202004009060 | 20040510 |
| WO 2004101017 | A2 | 20041125 | WO 2004-EP4985 | 20040510 |
| WO 2004101017 | A3 | 20050303 | | |

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,

SN, TD, TG

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| DE 202004009061 | U1 | 20040916 | DE 2004-202004009061 | 20040528 |
| WO 2004105826 | A2 | 20041209 | WO 2004-EP5785 | 20040528 |
| WO 2004105826 | A3 | 20050623 | | |

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|---|---|---|---|---|
| US 2005079200 | A1 | 20050414 | US 2004-938995 | 20040910 |
| US 2005079201 | A1 | 20050414 | US 2004-939021 | 20040910 |

PRIORITY APPLN. INFO.:

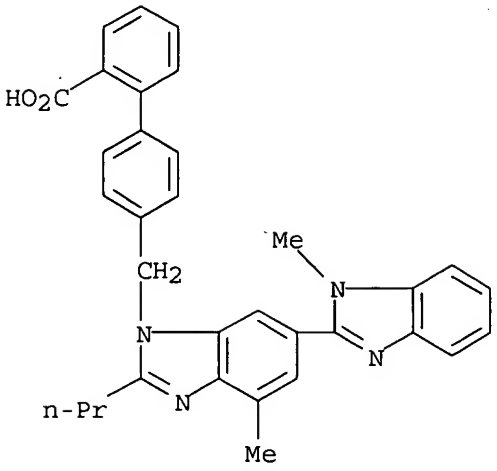
| | |
|---|---|
| DE 2003-10322182 | A1 20030516 |
| DE 2003-10324415 | A1 20030528 |
| DE 2003-10333098 | A1 20030721 |
| DE 2003-10333099 | A1 20030721 |
| WO 2004-EP4985 | A2 20040510 |
| WO 2004-EP5785 | A2 20040528 |

AB The invention concerns a method for the preparation of biocompatible coatings for implants, and medical goods composing the steps (a) coating the medical good at least partially with a polymer film using a coating **process**; (b) heating the polymer film in an oxygen-free atmospheric at 200-2500 °C to obtain a carbon layer on the medical good. The medical goods are heat resistant; they are prepared from carbon, carbon fibers, ceramics, glass, metals, alloys, artificial bone, stone, minerals; during heating they are transferred to their thermostable state. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, bone and joint prosthesis, artificial heart, heart valves, s.c., and i.m. implants can be coated. Other coating methods, e.g. dipping, spraying, printing can be applied. Several carbon layers with various porosity can be formed; biocompatible, biodegradable, non-biodegradable polymer layers can be placed on top of the carbon layers; drugs can be adsorbed onto the layers.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biocompatible coated medical implants with a carbon layer and method for preparation)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:965058 HCAPLUS
DOCUMENT NUMBER: 141:415987
TITLE: Preparation of **telmisartan** sodium salt for use in pharmaceutical formulations
INVENTOR(S): Kohlrausch, Anja
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2004096215 | A1 | 20041111 | WO 2004-EP4425 | | 20040427 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| DE 10319450 | A1 | 20041118 | DE 2003-10319450 | | 20030430 |
| US 2005004107 | A1 | 20050106 | US 2004-825580 | | 20040415 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10319450 | A | 20030430 |
| | | | US 2003-471675P | P | 20030519 |

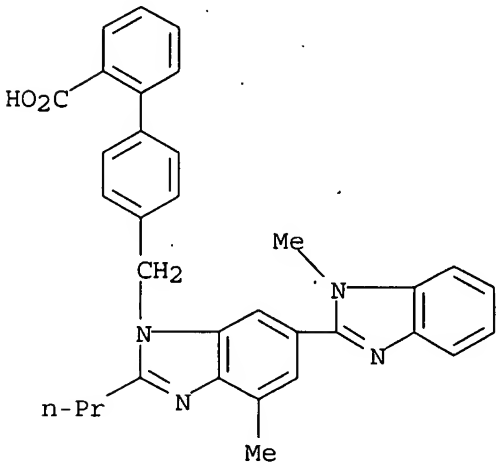
AB The invention relates to a medicament formulation of the crystalline sodium salt of 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid (**Telmisartan**) and methods for production thereof. **Telmisartan** sodium salt can also be formulated in combination with a diuretics, preferably hydrochlorothiazide. Thus two synthesis of crystalline **telmisartan**

sodium salt hemihydrate are described; the first one involves the reaction of **telmisartan** with sodium hydroxide in ethanol-containing toluene, followed by distillation of the solvent and crystallization In the second **process** first **telmisartan** hydrochloride is prepared from 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid tert. Bu ester; the product is then reacted with sodium methylate in toluene that also contains traces of water, isopropanol and methanol. Crystallization again is achieved by the azeotropic distillation of the solvents. A tablet contained (mg): **telmisartan** sodium salt 83.417; mannitol 299.083; microcryst. cellulose 100.000; croscarmellose sodium salt 10.000; magnesium stearate 7.500.

IT **515815-48-2P**, **Telmisartan** hydrochloride
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **telmisartan** sodium salt for use in pharmaceutical formulations)

RN 515815-48-2 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, monohydrochloride (9CI) (CA INDEX NAME)

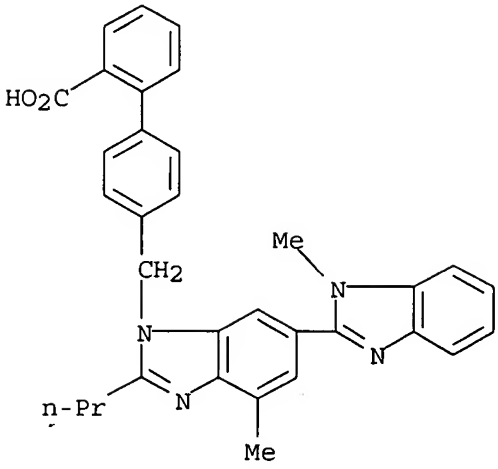



● HCl

IT **515815-49-3P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **telmisartan** sodium salt for use in pharmaceutical formulations)

RN 515815-49-3 HCAPLUS

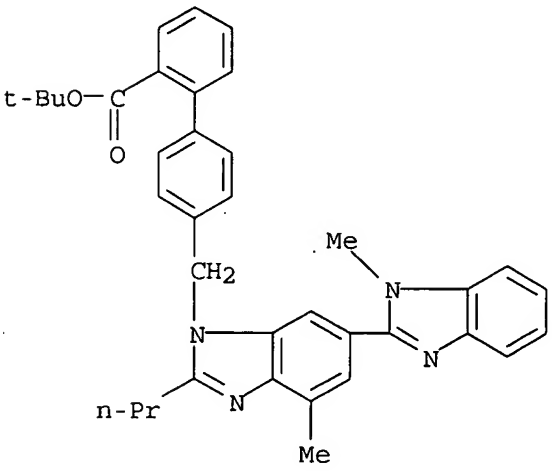
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, sodium salt, hydrate (2:1) (9CI) (CA INDEX NAME)



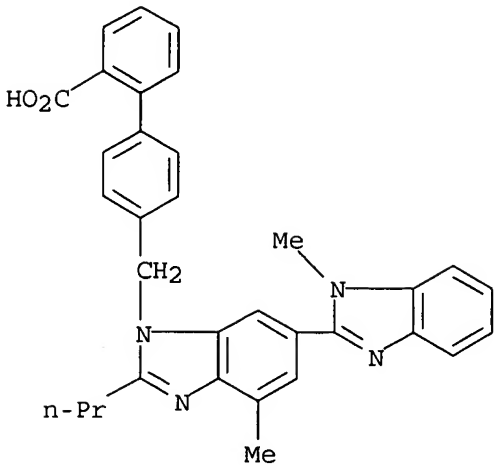
● 1/2 $H_2O$

● Na

IT **144702-26-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **telmisartan** sodium salt for use in pharmaceutical formulations)
RN 144702-26-1 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



IT **144701-48-4P, Telmisartan**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **telmisartan** sodium salt for use in pharmaceutical formulations)
RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

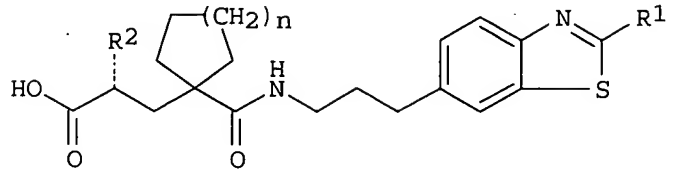
L17 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:759835 HCAPLUS
DOCUMENT NUMBER: 141:277616
TITLE: Preparation of 3-(1-[3-(1,3-benzothiazol-6-yl)propylcarbamoyl]cycloalkyl)propanoic acid derivatives as nep inhibitors
INVENTOR(S): Hepworth, David
PATENT ASSIGNEE(S): Pfizer Inc., UK
SOURCE: U.S. Pat. Appl. Publ., 27 pp., which
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004180941 | A1 | 20040916 | US 2004-800065 | 20040312 |
| WO 2004080985 | A1 | 20040923 | WO 2004-IB822 | 20040309 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| NL 1025709 | A1 | 20040916 | NL 2004-1025709 | 20040312 |
| NL 1025709 | C2 | 20050314 | | |

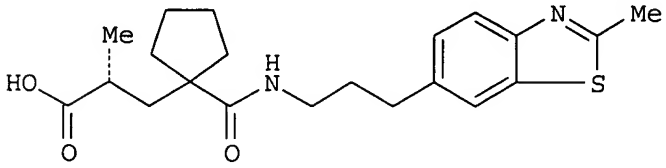
PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| GB 2003-5916 | A | 20030314 |
| US 2003-464608P | P | 20030422 |
| GB 2003-29143 | A | 20031216 |
| US 2004-538079P | P | 20040120 |

OTHER SOURCE(S): MARPAT 141:277616
GI



I



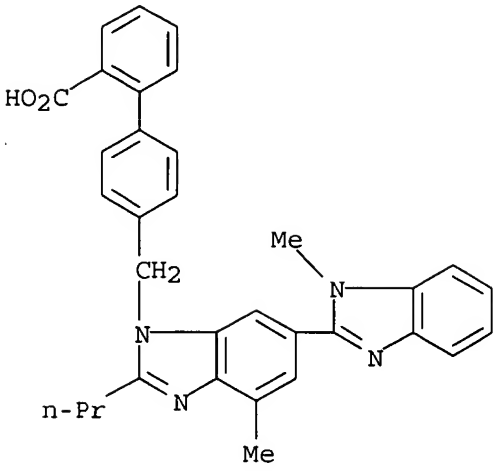
II

AB The invention relates to the use of title compds. I [R1 = H or Me; R2 = Me or Et; n = 1 or 2] as inhibitors of neutral endopeptidase enzyme (NEP), **processes** for the preparation thereof, intermediates used in the preparation thereof and compns. containing said inhibitors. Thus, e.g., II was prepared by amidation of 1-[(2R)-3-tert-butoxy-2-methyl-3-oxopropyl]cyclopentane carboxylic acid with 3-(2-methyl-1,3-benzothiazol-6-yl)propylamine dihydrochloride (preparation given) with subsequent hydrolysis to provide the free acid. I have been demonstrated to possess IC50 values of <20 nanomolar in tests for NEP inhibition and demonstrate a selectivity over soluble secreted endopeptidase (SEP) of at least 1000 fold. These inhibitors have utility in a variety of therapeutic areas including the treatment of male and female sexual dysfunction, particularly female sexual dysfunction (FSD), especially wherein the FSD is female sexual arousal disorder (FSAD).

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrug; preparation of ([(benzothiazolyl)propylcarbamoyl]cycloalkyl)propanoic acid derivs. as inhibitors of neutral endopeptidase enzyme)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)

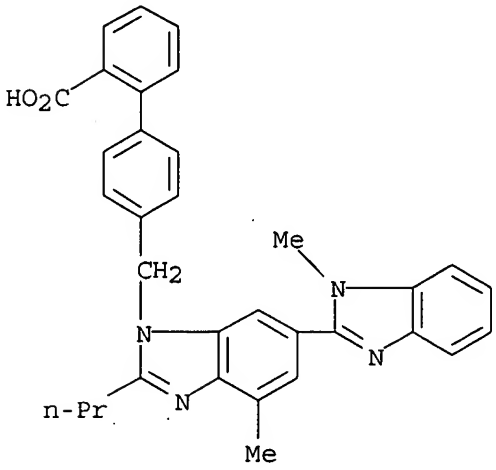


L17 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:756044 HCAPLUS
DOCUMENT NUMBER: 141:266048
TITLE: Medical implants with carbon-containing surfaces that are functionalized
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Gebrauchsmusterschrift, 18 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 202004009061 | U1 | 20040916 | DE 2004-202004009061 | 20040528 |
| DE 10324415 | A1 | 20041216 | DE 2003-10324415 | 20030528 |
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| DE 10333099 | A1 | 20050210 | DE 2003-10333099 | 20030721 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10324415 A1 | 20030528 |
| | | | DE 2003-10333098 A1 | 20030721 |
| | | | DE 2003-10333099 A1 | 20030721 |

AB The invention concerns medical implants with carbon-containing surfaces that are functionalized; the surfaces are prepared by (a) preparing a medical implant with a carbon-containing surface; (b) activation of the carbon layer by creating porosity; (c) functionalization of the activated, carbon-containing layer. The carbon layer can be prepared by pyrolysis, CVD, PVD, sputtering, ion implantation. The medical devices are prepared from carbon, carbon-composite material, glass, ceramics, glass fibers, carbon fibers, metals, stainless steel, titanium, tantalum, platinum, nitinol, alloys, artificial bone, minerals, and their combinations. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, artificial hearts and heart valves, artificial bones and joints are prepared The carbon layer is activated with oxidation or reducing agents in the presence of air, oxygen, nitrogen monoxide, oxidative acids; heat and/or ultrasound can be applied. The activated implant surfaces are functionalized with drugs, microorganisms, plant, animal or human cells. The invention also concerns controlled-release implanted drug delivery systems.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medical implants with carbon-containing surfaces that are functionalized)
RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:756043 HCAPLUS
DOCUMENT NUMBER: 141:266047
TITLE: Medical implants coated with biocompatible carbon-containing layers
PATENT ASSIGNEE(S): Blue Membranes GmbH, Germany
SOURCE: Ger. Gebrauchsmusterschrift, 23 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 202004009060 | U1 | 20040916 | DE 2004-202004009060 | 20040510 |
| DE 10322182 | A1 | 20041202 | DE 2003-10322182 | 20030516 |
| DE 10324415 | A1 | 20041216 | DE 2003-10324415 | 20030528 |
| DE 10333098 | A1 | 20050210 | DE 2003-10333098 | 20030721 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10322182 A1 | 20030516 |
| | | | DE 2003-10324415 A1 | 20030528 |
| | | | DE 2003-10333098 A1 | 20030721 |

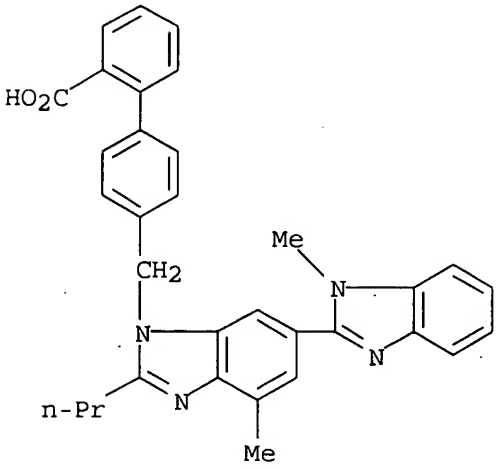
AB The invention concerns medical implants that are coated with biocompatible carbon-layers composed; the layers are prepared by (a) at least partial covering or coating of a medical implant with a polymer film; (b) heating the polymer film to 2000-2500°C in an oxygen-free atmospheric The medical device is prepared from carbon, carbon-composite material, glass, ceramics, glass fibers, carbon fibers, metals, stainless steel, titanium, tantalum, platinum, nitinol, alloys, artificial bone, minerals, and their combinations; during heat treatment they are transferred in their heat-stable modifications. Artificial blood vessels, stents, coronary stents, peripheral stents, orthopedic implants, artificial hearts and

heart valves, artificial bones and joints are prepared Polymers are applied by conventional coating techniques, e.g. from polymer solns.; carbon and silicon can be deposited in a PVD or CVD **process.** The biocompatible carbon layer can be coated with a bioresorbant or biodegradable polymer layer, e.g. polylactide. The implants can be loaded with drugs, microorganisms or cells.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medical implants coated with biocompatible carbon-containing layers)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:719056 HCAPLUS

DOCUMENT NUMBER: 142:85836

TITLE: A new topological descriptors based model for predicting intestinal epithelial transport of drugs in Caco-2 cell culture

AUTHOR(S): Ponce, Yovani Marrero; Perez, Miguel A. Cabrera; Zaldivar, Vicente Romero; Diaz, Humberto Gonzalez; Torrens, Francisco

CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical-Pharmacy, Central University of Las Villas, Santa Clara, 54830, Cuba

SOURCE: Journal of Pharmacy & Pharmaceutical Sciences (2004), 7(2), 186-199
CODEN: JPPSFY; ISSN: 1482-1826
URL: http://www.ualberta.ca/~csps/JPPS7(2)/Y.Ponce/caco-2.pdf

PUBLISHER: Canadian Society for Pharmaceutical Sciences

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

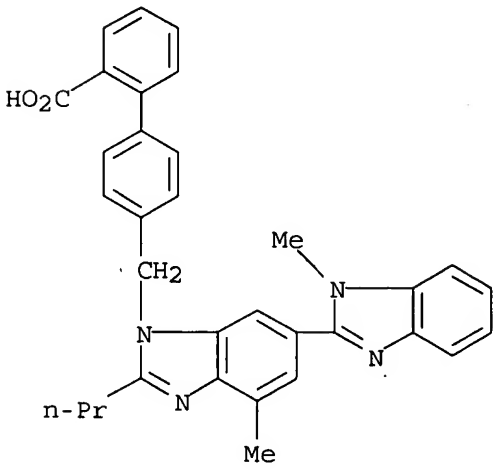
AB Purpose: Quant. Structure-Permeability Relationships (QSPerR) of the intestinal permeability across the (Caco-2) cells monolayer could be obtained by the application of new mol. descriptors. Method: A novel topol.-mol. approach to computer mol. design (TOMOCOMD-CARDD) has been used to estimate the intestinal-epithelial transport of drug in Caco-2 cell culture. Results: The Permeability Coeffs. in Caco-2 cells (P) for 33

structurally diverse drugs were well described using quadratic indexes of the mol. pseudograph's atom adjacency matrix as mol. descriptors. A quant. model that discriminates the high-absorption compds. from those with moderate-poor absorption was obtained for the training data set, showing a global classification of 87.87%. In addition, two QSPerR models, through a multiple linear regression, were obtained to predict the P [apical to basolateral (AP-BL) and basolateral to apical (BL-AP)]. A leave-n-out and leave-one-out cross-validation procedure revealed that the discriminant and regression models resp., had a good predictability. Furthermore, others 18 drugs were selected as a test set in order to assess. the predictive power of the models and the accuracy of the final prediction was similar to achieve for the data set. Besides, the use of both regression models, in a combinative way, is possible to predict the Permeability Directional Ratio (PDR, BL→AP/AP→BL) value.
The found models were used in virtual screening of drug intestinal permeability and a relationship between calculated P and percentage of human intestinal absorption for several compds. was established. Furthermore, this approximation permits us to obtain a good explanation of the experiment based
on the mol. structural features. Conclusions: These results suggest that the proposed method is able to predict the P values and it proved to be a good tool for studying the oral absorption of drug candidates during the drug development **process.**

IT **144701-48-4, Telmisartan**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(a new topol. descriptors based model for predicting intestinal epithelial transport of drugs in Caco-2 cell culture)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:528419 HCAPLUS
DOCUMENT NUMBER: 141:218304
TITLE: ADME Evaluation in Drug Discovery. 5. Correlation of Caco-2 Permeation with Simple Molecular Properties
AUTHOR(S): Hou, T. J.; Zhang, W.; Xia, K.; Qiao, X. B.; Xu, X. J.

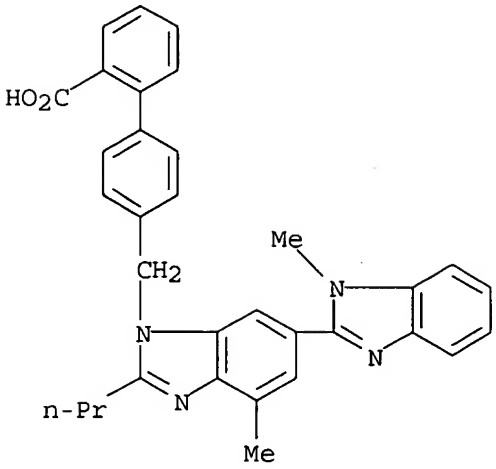
CORPORATE SOURCE: College of Chemistry and Molecular Engineering, Peking University, Beijing, 100871, Peop. Rep. China
SOURCE: Journal of Chemical Information and Computer Sciences (2004), 44(5), 1585-1600
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The correlations between Caco-2 permeability (logPapp) and mol. properties have been investigated. A training set of 77 structurally diverse organic mols. was used to construct significant QSAR models for Caco-2 cell permeation. Cellular permeation was found to depend primarily upon exptl. distribution coefficient (logD) at pH = 7.4, high charged polar surface area (HCPSA), and radius of gyration (rgyr). Among these three descriptors, logD may have the largest impact on diffusion through Caco-2 cell because logD shows obvious linear correlation with logPapp (r=0.703) when logD is smaller than 2.0. High polar surface area will be unfavorable to achieve good Caco-2 permeability because higher polar surface area will introduce stronger H-bonding interactions between Caco-2 cells and drugs. The comparison among HCPSA, PSA (polar surface area), and TPSA (topol. polar surface area) implies that high-charged atoms may be more important to the interactions between Caco-2 cell and drugs. Besides logD and HCPSA, rgyr is also closely connected with Caco-2 permeabilities. The mols. with larger rgyr are more difficult to cross Caco-2 monolayers than those with smaller rgyr. The descriptors included in the prediction models permit the interpretation in structural terms of the passive permeability **process**, evidencing the main role of lipoliphilicity, H-bonding, and bulk properties. Besides these three mol. descriptors, the influence of other mol. descriptors was also investigated. From the calculated results, it can be found that introducing descriptors concerned with mol. flexibility can improve the linear correlation. The resulting model with four descriptors bears good statistical significance, n = 77, r = 0.82, q = 0.79, s = 0.45, F = 35.7. The actual predictive abilities of the QSAR model were validated through an external validation test set of 23 diverse compds. The predictions for the tested compds. are as the same accuracy as the compds. of the training set and significantly better than those predicted by using the model reported. The good predictive ability suggests that the proposed model may be a good tool for fast screening of logPapp for compound libraries or large sets of new chemical entities via combinatorial chemical synthesis.

IT **144701-48-4, Telmisartan**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study)
(ADME evaluation in drug discovery)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:189973 HCAPLUS
DOCUMENT NUMBER: 141:235641
TITLE: Total and local quadratic indices of the "molecular pseudograph's atom adjacency matrix". Application to prediction of Caco-2 permeability of drugs
AUTHOR(S): Ponce, Yovani Marrero; Perez, Miguel Angel Cabrera; Zaldivar, Vicente Romero; Ofori, Ernest; Montero, Luis A.
CORPORATE SOURCE: Department of Pharmacy, Faculty of Chemical-Pharmacy, Central University of Las Villas, Villa Clara, 54830, Cuba
SOURCE: International Journal of Molecular Sciences (2003), 4(8/9), 512-536
CODEN: IJMCFK; ISSN: 1422-0067
URL: http://www.mdpi.org/ijms/papers/i4080512.pdf
PUBLISHER: Molecular Diversity Preservation International
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

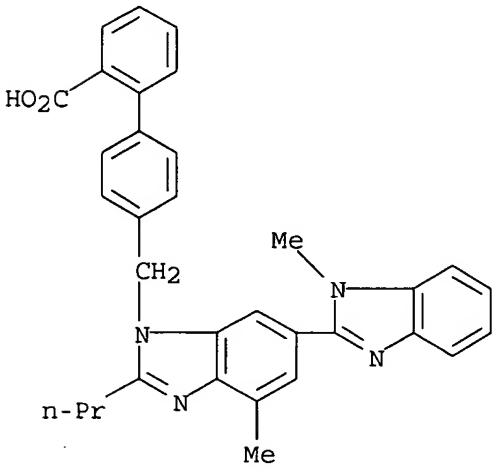
AB The high interest in the prediction of the intestinal absorption for New Chemical Entities (NCEs) is generated by the increasing rate in the synthesis of compds. by combinatorial chemical and the extensive cost of the traditional evaluation methods. Quant. Structure-Permeability Relationships (QSPerR) of the intestinal permeability across the Caco-2 cells monolayer (PCaco-2) could be obtained by the application of new mol. descriptors. In this sense, quadratic indexes of the "mol. pseudograph's atom adjacency matrix" and multiple linear regression anal. were used to obtain good quant. models to determine the PCaco-2. QSPerR models found are significant from a statistical point of view. The total and local quadratic indexes were calculated with the TOMO-COMD software. A leave-one-out cross-validation procedure (internal validation) and the evaluation of external test set of 20 drugs (external validation) revealed that regression models had a good predictive power. A comparison with results derived from other theor. studies shown a quite satisfactory behavior of the present method. The descriptors included in the prediction models permitted the interpretation in structural terms of the permeability **process**, evidencing the main role of H-bonding and

size properties. The models found were used in virtual screening of drug intestinal permeability and a relationship between PCaco-2 calculated and percentage of human intestinal absorption for the 72 compds. was established. These results suggest that the proposed method is able to predict PCaco-2, being a good tool for screening of Pcaco-2 for large sets of NCEs synthesized via combinatorial chemical approach.

IT **144701-48-4, Telmisartan**
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(total and local quadric indexes were calculated with TOMO-COMD software was found to be good tool)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:99589 HCAPLUS

DOCUMENT NUMBER: 140:309530

TITLE: Prediction of MS/MS Data. 1. a focus on pharmaceuticals containing carboxylic acids

AUTHOR(S): Bandu, Mary L.; Watkins, Kathryn R.; Bretthauer, Melinda L.; Moore, Christopher A.; Desaire, Heather

CORPORATE SOURCE: Department of Chemistry, University of Kansas, Lawrence, KS, 66045, USA

SOURCE: Analytical Chemistry (2004), 76(6), 1746-1753
CODEN: ANCHAM; ISSN: 0003-2700

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

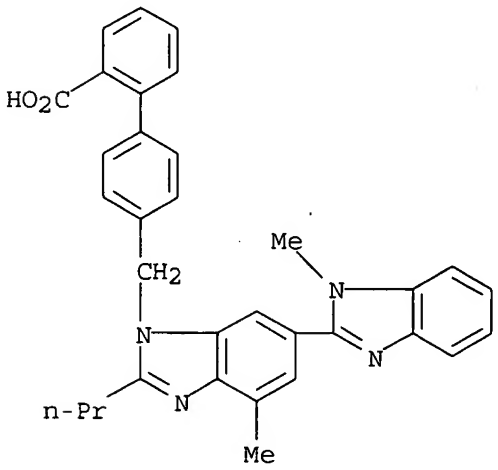
AB Metabolite identification is a necessary step in developing safe and effective drugs. Metabolite anal. typically involves rapid identification of the chemical composition of the metabolite by automated HPLC-MS methods, followed by the laborious **process** of identifying the structure of the metabolite. Since MS is typically utilized to identify the metabolite, it is logical to utilize MS/MS to structurally characterize the sample. However, interpretation of MS/MS data may not provide sufficient information, as fragmentation pathways are not well understood

or predictable. Therefore, other more time-consuming methods of anal. are often undertaken. If the dissociation rules for low-energy MS/MS expts. were clearly defined for all classes of compds., more information would be obtained from MS/MS data, and metabolite identification would proceed more rapidly. We are currently developing methods to define these fragmentation rules. By screening .apprx.100 carboxylic acids at a time and applying knowledge of phys.-organic chemical, predictive rules are under development that describe how compds. dissociate under low-energy collision-induced dissociation conditions. Studies of carboxylic acid dissociation demonstrate that this approach is practical and reliable. Dissociation rules were predicted with a 90% success rate, when tested on acid-containing pharmaceuticals. This predictive power cannot be matched by any com. available software. This study, and others like it, will be used to develop algorithms that more rapidly identify drug metabolites and degradation products, based on MS/MS data. Such algorithms will benefit drug development for all types of pharmaceuticals.

IT **144701-48-4, Telmisartan**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(prediction of MS/MS Data for pharmaceuticals containing carboxylic acids)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:700804 HCAPLUS

DOCUMENT NUMBER: 140:28746

TITLE: Synthesis of **telmisartan**

AUTHOR(S): Fu, Yan; Guo, Yi; Yang, Shuang-ge; Chen, Li-li; Yan, Li-xue

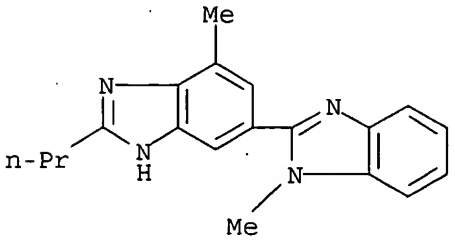
CORPORATE SOURCE: Faculty of Medicinal Chemistry, Pharmaceutical Science College, Hebei Medical University, Shijiazhuang, 050017, Peop. Rep. China

SOURCE: Zhongguo Xinyao Zazhi (2003), 12(7), 538-539
CODEN: ZXZHA6; ISSN: 1003-3734

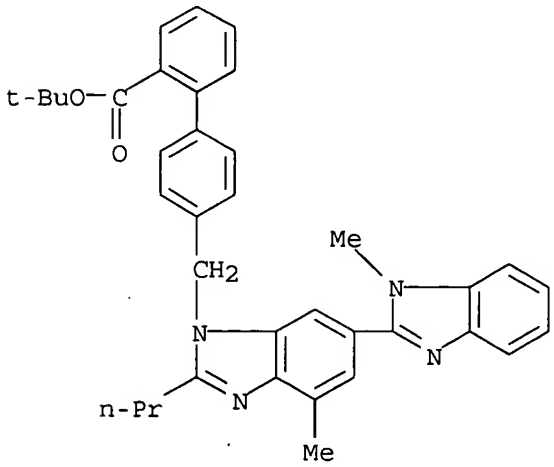
PUBLISHER: Zhongguo Xinyao Zazhishe

DOCUMENT TYPE: Journal

LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 140:28746
AB The title compound was prepared from 7-methyl-2-propyl-1H-benzimidazole-5-carboxylic acid by cyclocondensation with N-methyl-o-phenylenediamine, alkylation with t-Bu 4'-(bromomethyl)biphenyl-2-carboxylate and hydrolysis. The overall yield was 45.6%. The **process** gives improved yield and decreased cost.
IT **152628-02-9P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation and alkylation with t-Bu (bromomethyl)biphenylcarboxylate)
RN 152628-02-9 HCAPLUS
CN 2,5'-Bi-1H-benzimidazole, 1,7'-dimethyl-2'-propyl- (9CI) (CA INDEX NAME)

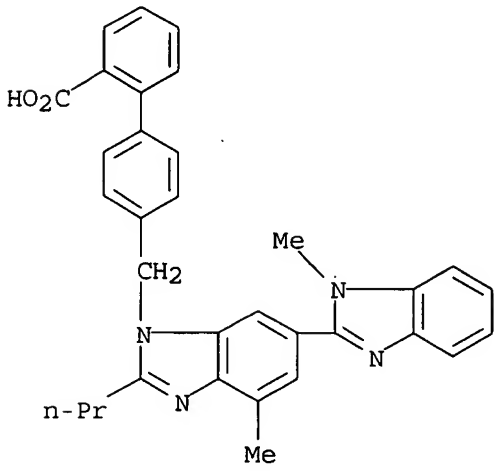



IT **144702-26-1P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)
RN 144702-26-1 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)




IT **144701-48-4P, Telmisartan**
RL: CPS (Chemical process); IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PREP (Preparation); PROC (Process)
(**process** for production of)
RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-

benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:754995 HCAPLUS
DOCUMENT NUMBER: 137:268473
TITLE: Porous drug matrices and methods of manufacture thereof
INVENTOR(S): Straub, Julie; Altreuter, David; Bernstein, Howard; Chickering, Donald E.; Khattak, Sarwat; Randall, Greg
PATENT ASSIGNEE(S): Acusphere Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U. S. 6,395,300.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2002142050 | A1 | 20021003 | US 2002-53929 | | 20020122 |
| US 6395300 | B1 | 20020528 | US 1999-433486 | | 19991104 |
| US 6645528 | B1 | 20031111 | US 2000-694407 | | 20001023 |
| US 6932983 | B1 | 20050823 | US 2000-706045 | | 20001103 |
| ZA 200101047 | A | 20030730 | ZA 2001-10347 | | 20011218 |
| US 2005048116 | A1 | 20050303 | US 2004-924642 | | 20040824 |
| US 2005058710 | A1 | 20050317 | US 2004-928886 | | 20040827 |
| PRIORITY APPLN. INFO.: | | | US 1999-136323P | P | 19990527 |
| | | | US 1999-158659P | P | 19991008 |
| | | | US 1999-433486 | A2 | 19991104 |
| | | | US 2002-53929 | A3 | 20020122 |

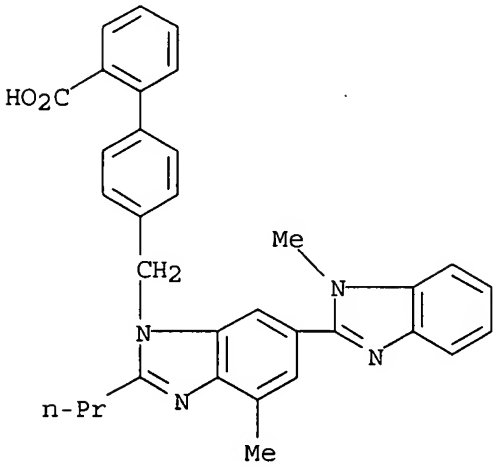
AB Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aqueous media. The drug matrixes preferably are made using a **process** that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion,

suspension, or second solution and hydrophilic or hydrophobic excipients that stabilize the drug and inhibit crystallization, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. Hydrophobic or hydrophilic excipients may be selected to stabilize the drug in crystalline form by inhibiting crystal growth or to stabilize the drug in amorphous form by preventing crystallization The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration. Thus, 5.46 g of PEG 8000, 0.545 g of prednisone, and 0.055 g of Span 40 were dissolved in 182 mL of methylene chloride. A solution of 3.27 g of ammonium bicarbonate in 18.2 mL of water was added to the organic solution (phase ratio 1:10) and homogenized for 5 min at 16,000 RPM. The resulting emulsion was spray dried on a benchtop spray dryer using an air-atomizing nozzle and nitrogen as the drying gas.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(porous drug matrixes and methods of manufacture thereof)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:750331 HCAPLUS

DOCUMENT NUMBER: 139:62535

TITLE: Rate-Limited Steps of Human Oral Absorption and QSAR Studies

AUTHOR(S): Zhao, Yuan H.; Abraham, Michael H.; Le, Joelle; Hersey, Anne; Luscombe, Chris N.; Beck, Gordon; Sherborne, Brad; Cooper, Ian

CORPORATE SOURCE: Department of Chemistry, University College London,

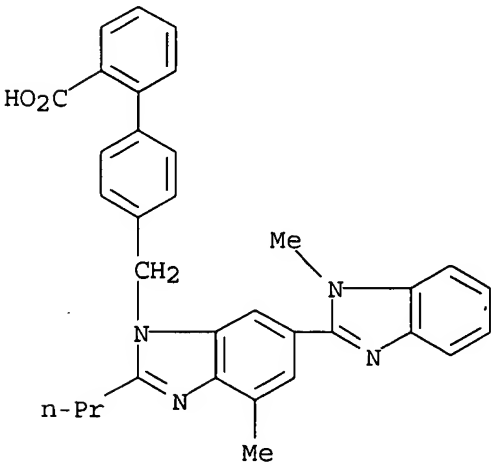
London, WC1H 0AJ, UK
SOURCE: Pharmaceutical Research (2002), 19(10), 1446-1457
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose. To classify the dissoln. and diffusion rate-limited drugs and establish quant. relationships between absorption and mol. descriptors. Methods. Absorption consists of kinetic transit **processes** in which dissoln., diffusion, or perfusion **processes** can become the rate-limited step. The absorption data of 238 drugs have been classified into either dissoln. or diffusion rate-limited based on an equilibrium method developed from solubility, dose, and percentage of absorption. A nonlinear absorption model derived from first-order kinetics has been developed to identify the relationship between percentage of drug absorption and mol. descriptors. Results. Regression anal. was performed between percentage of absorption and mol. descriptors. The descriptors used were ClogP, mol. polar surface area, the number of hydrogen-bonding acceptors and donors, and Abraham descriptors. Good relationships were found between absorption and Abraham descriptors or ClogP. Conclusions. The absorption models can predict the following three BCS (Biopharmaceutics Classification Scheme) classes of compds.: class I, high solubility and high permeability; class III, high solubility and low permeability; class IV, low solubility and low permeability.

The absorption models overpredict the absorption of class II, low solubility and high permeability compds. because dissoln. is the rate-limited step of absorption.

IT **144701-48-4, Telmisartan**
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rate-limited steps of human oral absorption and QSAR studies)

RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:736138 HCAPLUS

DOCUMENT NUMBER: 137:253025
TITLE: **Process** for producing sustained release preparation
INVENTOR(S): Shiraishi, Keiko; Yamagata, Yutaka; Hata, Yoshio
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

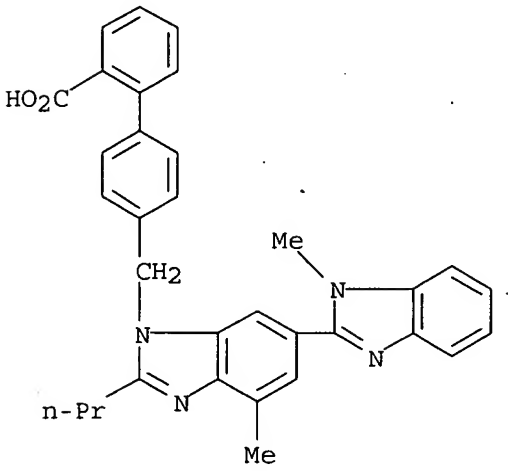
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002074340 | A1 | 20020926 | WO 2002-JP2404 | 20020314 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1369130 | A1 | 20031210 | EP 2002-705171 | 20020314 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003212758 | A2 | 20030730 | JP 2002-72124 | 20020315 |
| US 2004121008 | A1 | 20040624 | US 2003-471736 | 20030915 |
| PRIORITY APPLN. INFO.: | | | JP 2001-77157 A | 20010316 |
| | | | JP 2001-353757 A | 20011119 |
| | | | WO 2002-JP2404 W | 20020314 |

OTHER SOURCE(S): MARPAT 137:253025

AB Disclosed are a **process** for producing a sustained release preparation characterized by comprising removing a solvent from an organic solvent solution containing a hardly water soluble nonpeptidic physiol. active compound, a polyvalent metal compound and a biodegradable polymer in an amount exceeding the solubility of the biodegradable polymeric in the organic solvent in the absence of the polyvalent metal compound; sustained release prepns. obtained by the above production **process**; sustained release solid medicinal compns. containing a nonpeptidic physiol. active substance and a biodegradable polymer, wherein about 0.05% by weight, based on the composition weight, or more of a polyvalent metal is present on the composition surface; etc. In these sustained release prepns., the hardly water-soluble nonpeptidic physiol. active compound is uniformly distributed and the sustained release effect of the hardly water-soluble nonpeptidic physiol. active compound can be stably achieved. Moreover, medicinal compns. containing a nonpeptidic physiol. active substance wherein the early release of the physiol. active substance is efficiently controlled, a **process** for producing the same, etc. are provided. For example, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid 2 g, zinc acetate dihydrate 0.996 g, and polylactic acid 3.67 g were dissolved in dichloromethane/methanol mixture The solution was added to an aqueous solution of polyvinyl alc. to give an O/W emulsion, which was worked up to obtain sustained-release microcapsules.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**process** for producing sustained release preparation using biodegradable polymers)
RN 144701-48-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:617864 HCAPLUS
DOCUMENT NUMBER: 135:185483
TITLE: Sustained-release compositions of physiologically active compounds hardly-soluble in water and production **process** and use of the same
INVENTOR(S): Kamei, Shigeru; Ojima, Mami; Kitayoshi, Takahito; Igari, Yasutaka
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001060410 | A1 | 20010823 | WO 2001-JP1191 | 20010220 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2400845 | AA | 20010823 | CA 2001-2400845 | 20010220 |
| AU 2001032348 | A5 | 20010827 | AU 2001-32348 | 20010220 |
| EP 1258254 | A1 | 20021120 | EP 2001-904560 | 20010220 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

| | | | | |
|---|---|---|---|---|
| JP 2001316296 | A2 | 20011113 | JP 2001-44602 | 20010221 |
| US 2003068374 | A1 | 20030410 | US 2002-204185 | 20020819 |
| PRIORITY APPLN. INFO.: | | | JP 2000-48980 A | 20000221 |
| | | | WO 2001-JP1191 W | 20010220 |

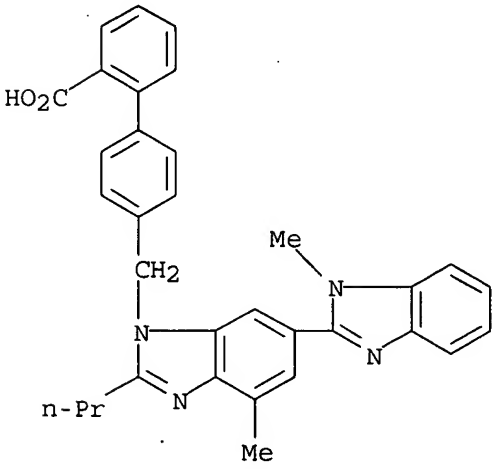
OTHER SOURCE(S): MARPAT 135:185483

AB Disclosed are sustained-release prepns. containing a physiol. active substance hardly soluble in water, a component obtained by treating with water a polyvalent metal compound hardly soluble in water and a biodegradable polymer which are improved in the release-control and stabilization of the physiol. active substance hardly soluble in water and can be produced by a **process** suitable for mass production Sustained-release microcapsules were formulated from candesartan, zinc oxide, glycolic acid-lactic acid copolymer.

IT **144701-48-4, Telmisartan**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release compns. containing physiol. active compds. hardly-soluble in water, polyvalent metal compds., and biodegradable polymers)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2000:861473 HCAPLUS |
| DOCUMENT NUMBER: | 134:32972 |
| TITLE: | Porous drug matrixes containing polymers and sugars and methods of their manufacture |
| INVENTOR(S): | Straub, Julie; Bernstein, Howard; Chickering, Donald E., III; Khatak, Sarwat; Randall, Greg |
| PATENT ASSIGNEE(S): | Acusphere, Inc., USA |
| SOURCE: | PCT Int. Appl., 45 pp.<br>CODEN: PIXXD2 |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | English |
| FAMILY ACC. NUM. COUNT: | 2 |
| PATENT INFORMATION: | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2000072827 | A2 | 20001207 | WO 2000-US14578 | | 20000525 |
| WO 2000072827 | A3 | 20010125 | | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | |
| US 6395300 | B1 | 20020528 | US 1999-433486 | | 19991104 |
| CA 2371836 | AA | 20001207 | CA 2000-2371836 | | 20000525 |
| EP 1180020 | A2 | 20020220 | EP 2000-939365 | | 20000525 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | | |
| BR 2000010984 | A | 20020430 | BR 2000-10984 | | 20000525 |
| JP 2003500438 | T2 | 20030107 | JP 2000-620939 | | 20000525 |
| NZ 516083 | A | 20030829 | NZ 2000-516083 | | 20000525 |
| AU 768022 | B2 | 20031127 | AU 2000-54459 | | 20000525 |
| US 2002041896 | A1 | 20020411 | US 2001-798824 | | 20010302 |
| US 6610317 | B2 | 20030826 | | | |
| NO 2001005753 | A | 20020128 | NO 2001-5753 | | 20011126 |
| ZA 2001010347 | A | 20030730 | ZA 2001-10347 | | 20011218 |
| PRIORITY APPLN. INFO.: | | | US 1999-136323P | P | 19990527 |
| | | | US 1999-158659P | P | 19991008 |
| | | | US 1999-433486 | A | 19991104 |
| | | | US 2000-186310P | P | 20000302 |
| | | | WO 2000-US14578 | W | 20000525 |

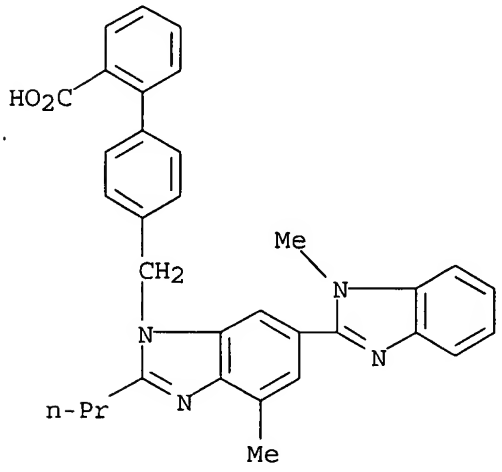
AB Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissoln. of the drug in aqueous media. The drug matrixes preferably are made using a **process** that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solns., and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissoln. following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration. Paclitaxel or docetaxel can be provided in a porous matrix form, which allows the drug to be formulated without solubilizing agents and administered as a bolus. For example, a nifedipine-loaded organic solution was prepared by dissolving 9.09 g of PEG 3350, 2.27 g of nifedipine, and 0.009 g of lecithin in 182 mL of methylene chloride. An aqueous solution was prepared by dissolving 3.27 g of NH4HCO3 and 0.91 g of PEG 3350 in 1.82 mL of water. The aqueous and organic solns. were homogenized and resulting emulsion

was spray dried. A suspension of the porous nifedipine drug matrix was prepared in 5% dextrose solution at a concentration of 2.5 mg/mL. A bolus injection of the suspension was tolerated when administrated to dogs.

IT **144701-48-4, Telmisartan**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preparation of porous matrixes containing hydrophilic polymers and sugars for enhancement of drug dissoln.)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




L17 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:226459 HCAPLUS

DOCUMENT NUMBER: 132:342771

TITLE: Evaluation of an accelerated Caco-2 cell permeability model

AUTHOR(S): Liang, Earvin; Chessic, Kelli; Yazdanian, Mehran

CORPORATE SOURCE: Pharmaceutics Department, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, 06877, USA

SOURCE: Journal of Pharmaceutical Sciences (2000), 89(3), 336-345
CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

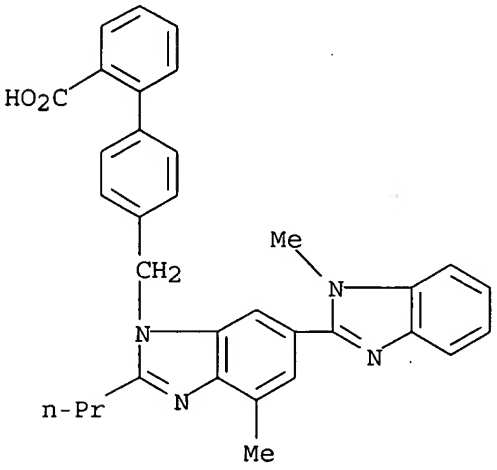
AB An accelerated 3-7 day Caco-2 cell permeability model was examined and compared to the traditional 21-25 day model. Caco-2 cell permeability coeffs. (PCaco-2) of 33 structurally diverse small mol. weight compds. from apical to basolateral (AP→BL) direction in the accelerated model were approx. twice those in the traditional model. As observed with microscopy and transepithelial elec. resistance measurements, this difference was attributed to less confluent and differentiated Caco-2 cell monolayers in the accelerated model. However, there were no significant differences in rank ordering of the compds. The expression of P-glycoprotein in the accelerated model was shown to be significantly less than that in the traditional model. This resulted in lower permeability

directional ratios defined as the ratio between permeability coeffs. from BL→AP and from AP→BL for compds. that were cellular efflux pump substrates. The accelerated model may not be suitable for studying cellular efflux pumps such as P-glycoproteins. However, it is a feasible alternative to the traditional model for rank ordering of compds. in the **process** of drug discovery and development by significantly improving the turnover time and labor efficiency. This makes it an excellent Caco-2 cell permeability model for high through-put screening.

IT **144701-48-4, Telmisartan**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(evaluation of accelerated Caco-2 cell permeability model of intestinal transepithelial transport and role of P-glycoproteins and drug screening)

RN 144701-48-4 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL REGISTRY

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 221.16 | 727.84 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -34.31 | -34.31 |

FILE 'REGISTRY' ENTERED AT 14:24:47 ON 30 OCT 2005


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 OCT 2005 HIGHEST RN 866391-97-1

DICTIONARY FILE UPDATES: 28 OCT 2005 HIGHEST RN 866391-97-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

**********
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
**********

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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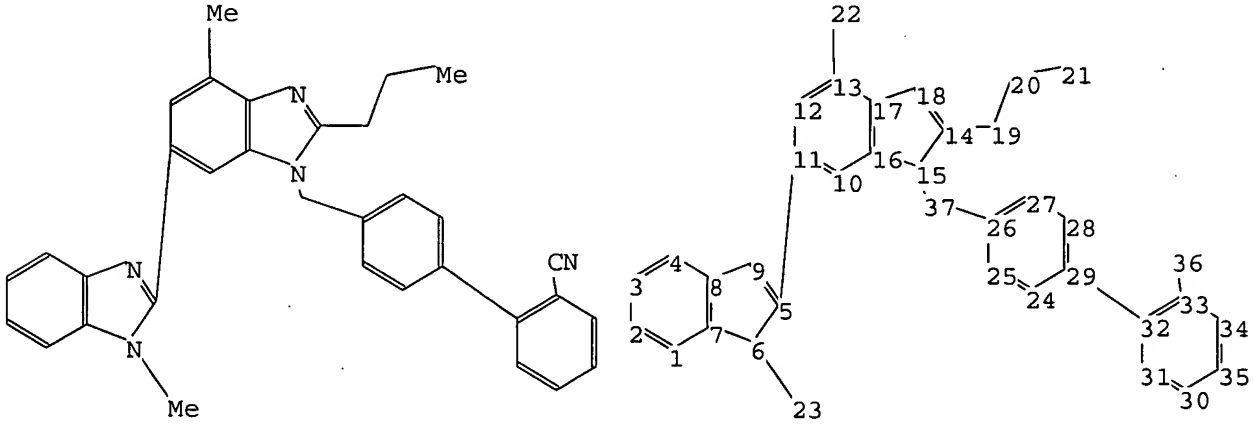
Uploading C:\Program Files\Stnexp\Queries\10802142c.str



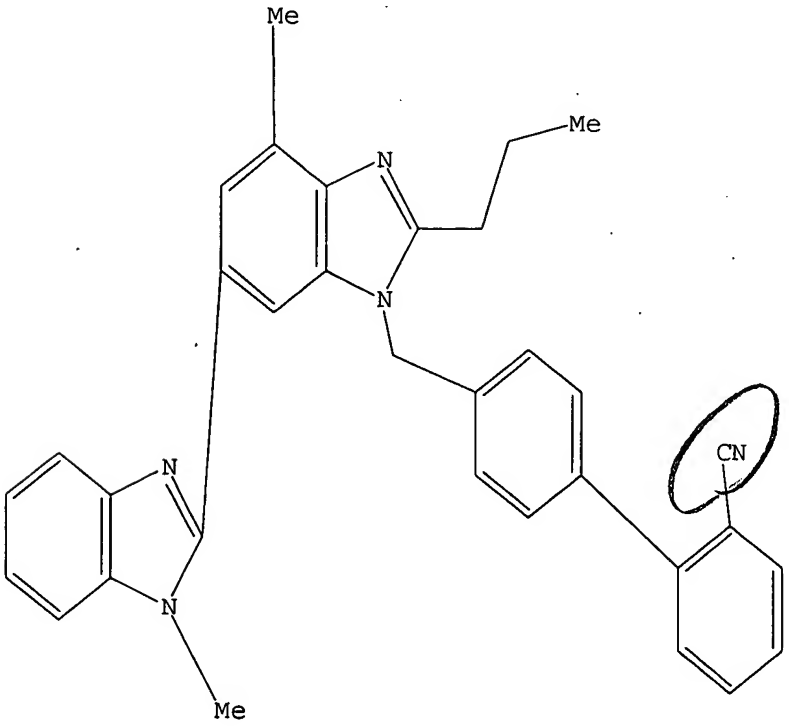

chain nodes :
19 20 21 22 23 36 37
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 24 25 26 27 28 29 30 31 32 33 34 35

chain bonds :
5-11 6-23 13-22 14-19 15-37 19-20 20-21 26-37 29-32 33-36
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 10-11 10-16 11-12 12-13 13-17
14-15 14-18 15-16 16-17 17-18 24-25 24-29 25-26 26-27 27-28 28-29 30-31
30-35 31-32 32-33 33-34 34-35
exact/norm bonds :
5-6 5-9 6-7 8-9 14-15 14-18 15-16 15-37 17-18
exact bonds :
5-11 6-23 13-22 14-19 19-20 20-21 26-37 29-32 33-36
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8 10-11 10-16 11-12 12-13 13-17 16-17 24-25
24-29 25-26 26-27 27-28 28-29 30-31 30-35 31-32 32-33 33-34 34-35
isolated ring systems :
containing 24 : 30 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom
29:Atom 30:Atom 31:Atom 32:Atom 33:Atom 34:Atom 35:Atom 36:CLASS 37:CLASS

L18 STRUCTURE UPLOADED

=> d l18
L18 HAS NO ANSWERS
L18 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l18
SAMPLE SEARCH INITIATED 14:25:11 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        4 TO ITERATE

100.0% PROCESSED         4 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            4 TO      200
PROJECTED ANSWERS:               0 TO        0

L19             0 SEA SSS SAM L18

=> s l18 sss full
FULL SEARCH INITIATED 14:25:19 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       83 TO ITERATE

100.0% PROCESSED        83 ITERATIONS                               1 ANSWERS
SEARCH TIME: 00.00.01

L20             1 SEA SSS FUL L18

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Uploading C:\Program Files\Stnexp\Queries\10802142d.str
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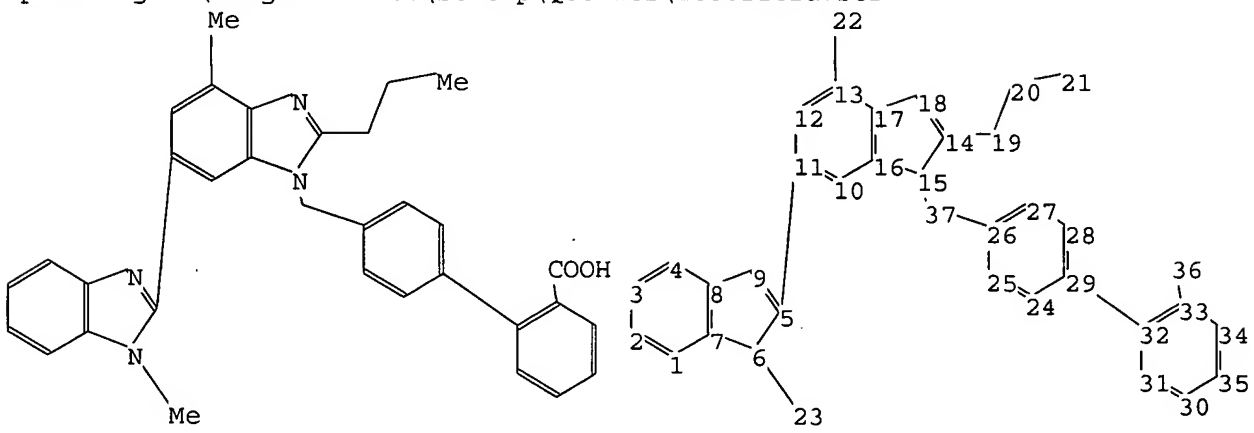


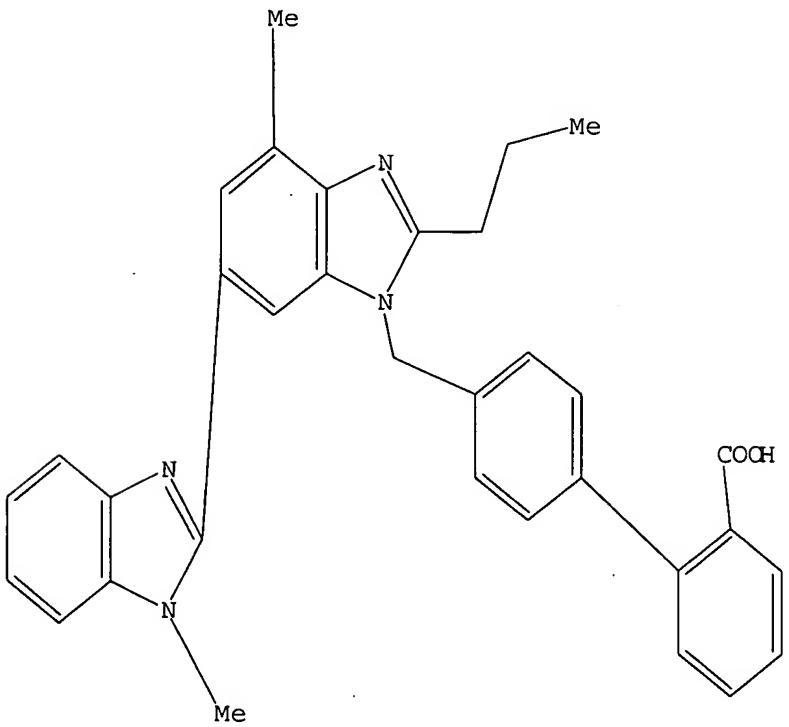

```
chain nodes :
19  20  21  22  23  36  37
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  24  25  26  27  28
29  30  31  32  33  34  35
chain bonds :
```

5-11 6-23 13-22 14-19 15-37 19-20 20-21 26-37 29-32 33-36
ring bonds :
1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 10-11 10-16 11-12 12-13 13-17
14-15 14-18 15-16 16-17 17-18 24-25 24-29 25-26 26-27 27-28 28-29 30-31
30-35 31-32 32-33 33-34 34-35
exact/norm bonds :
5-6 5-9 6-7 8-9 14-15 14-18 15-16 15-37 17-18
exact bonds :
5-11 6-23 13-22 14-19 19-20 20-21 26-37 29-32 33-36
normalized bonds :
1-2 1-7 2-3 3-4 4-8 7-8 10-11 10-16 11-12 12-13 13-17 16-17 24-25
24-29 25-26 26-27 27-28 28-29 30-31 30-35 31-32 32-33 33-34 34-35
isolated ring systems :
containing 24 : 30 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom
29:Atom 30:Atom 31:Atom 32:Atom 33:Atom 34:Atom 35:Atom 36:CLASS 37:CLASS

L21 STRUCTURE UPLOADED

=> d l21
L21 HAS NO ANSWERS
L21 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l21
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SAMPLE SCREEN SEARCH COMPLETED -       10 TO ITERATE

100.0% PROCESSED       10 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           11 TO      389
PROJECTED ANSWERS:               3 TO      163

L22           3 SEA SSS SAM L21

=> s l21 sss full
FULL SEARCH INITIATED 14:27:11 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      197 TO ITERATE

100.0% PROCESSED      197 ITERATIONS                               30 ANSWERS
SEARCH TIME: 00.00.01

L23          30 SEA SSS FUL L21

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   323.52    1051.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -34.31

FILE 'HCAPLUS' ENTERED AT 14:27:19 ON 30 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 30 Oct 2005  VOL 143 ISS 19
FILE LAST UPDATED: 28 Oct 2005  (20051028/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

```
=> d his

     (FILE 'HOME' ENTERED AT 14:06:55 ON 30 OCT 2005)

     FILE 'REGISTRY' ENTERED AT 14:07:04 ON 30 OCT 2005
L1             STRUCTURE UPLOADED
L2           1 S L1
L3          28 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:07:31 ON 30 OCT 2005
L4         231 S L3

     FILE 'REGISTRY' ENTERED AT 14:12:40 ON 30 OCT 2005
L5             STRUCTURE UPLOADED
L6           0 S L5
L7           0 S L5 SSS FULL
L8             STRUCTURE UPLOADED
L9           4 S L8
L10         97 S L8 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:14:39 ON 30 OCT 2005
L11        397 S L10
L12          3 S L4 AND L11
L13        375 S L11 AND TELMISARTAN
L14        442 S TELMISARTAN
L15         23 S L14 AND PROCESS
L16          0 S L4 AND L15
L17         21 S L11 AND L15

     FILE 'REGISTRY' ENTERED AT 14:24:47 ON 30 OCT 2005
L18            STRUCTURE UPLOADED
L19          0 S L18
L20          1 S L18 SSS FULL
L21            STRUCTURE UPLOADED
L22          3 S L21
L23         30 S L21 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 14:27:19 ON 30 OCT 2005

=> s l21
   REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.



SAMPLE SEARCH INITIATED 14:27:46 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       10 TO ITERATE

100.0% PROCESSED       10 ITERATIONS                          3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           11 TO      389
PROJECTED ANSWERS:               3 TO      163
```

L24 3 SEA SSS SAM L21

L25 4 L24

=> s l20
L26 3 L20

=> s l23
L27 390 L23

=> d l26 ibib abs hitstr tot

L26 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:858350 HCAPLUS
DOCUMENT NUMBER: 142:316836
TITLE: Preparation of telmisartan
INVENTOR(S): Shen, Jingshan; Yan, Tiema; Liu, Weisi; Mao, Rui; Li, Jianfeng; Ji, Ruyun
PATENT ASSIGNEE(S): Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China; Tehua Medicine and Chemicals Co., Ltd., Shanghai
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 7 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

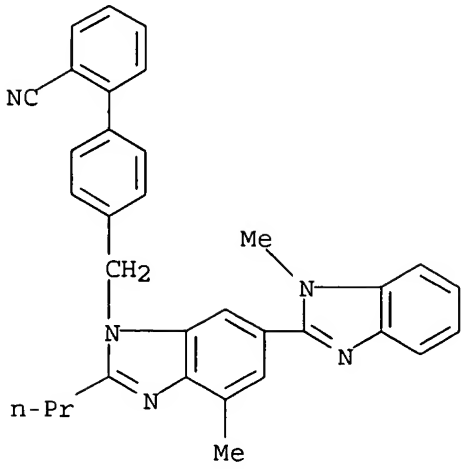
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 1412183 | A | 20030423 | CN 2001-131915 | 20011015 |
| PRIORITY APPLN. INFO.: | | | CN 2001-131915 | 20011015 |

OTHER SOURCE(S): CASREACT 142:316836

AB The method comprises substituting 4-methyl-5-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazole with 4-(2-cyanophenyl)benzyl bromide in solvent in the presence of acid capturing agent at 20-80° for 4-6 h and then hydrolyzing with acid in C1-5 alc.-water or other solvent at 30-160° for 10-20 h. The acid capturing agent is Na alkoxide, triethylamine, tributylamine, tripropylamine, NaOH, KOH, Ca(OH)2, etc. The solvent is DMF, DMSO, THF, dioxane, acetone, etc. The acid is H2SO4, HCl, HBr, and/or glacial acetic acid.

IT **144702-27-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of telmisartan)

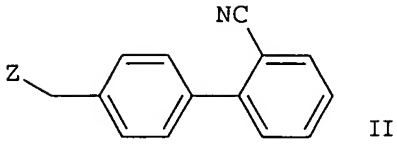
RN 144702-27-2 HCAPLUS
CN [1,1'-Biphenyl]-2-carbonitrile, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]- (9CI) (CA INDEX NAME)




L26 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:857574 HCAPLUS
DOCUMENT NUMBER: 141:332194
TITLE: Preparation of Telmisartan by reaction of 2-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)benzimidazole with 4-bromomethyl-2'-cyanobiphenyl or related compounds followed by hydrolysis.
INVENTOR(S): Hauel, Norbert; Dach, Rolf; Heitger, Helmut; Meyer, Oliver
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma GmbH & Co. Kg
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004087676 | A1 | 20041014 | WO 2004-EP3217 | 20040326 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10314702 | A1 | 20041021 | DE 2003-10314702 | 20030331 |
| US 2004236113 | A1 | 20041125 | US 2004-802142 | 20040317 |
| PRIORITY APPLN. INFO.: | | | DE 2003-10314702 A | 20030331 |
| | | | US 2003-465952P P | 20030428 |

OTHER SOURCE(S): CASREACT 141:332194; MARPAT 141:332194
GI



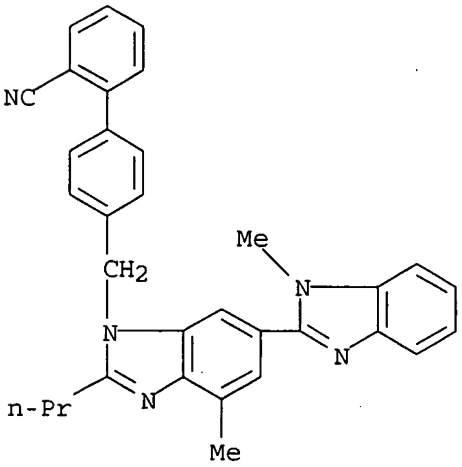

II

AB Telmisartan was prepared by reaction of 2-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)benzimidazole (I) with biphenyl derivative (II; Z = leaving group) followed by hydrolysis. Thus, I was stirred 1 h with KOCMe3 in dimethylacetamide; II (X = Br) in dimethylacetamide was added over 30 min. followed by cooling, removal of solvent in vacuo, and crystn from MeOCMe3 to give 87.5% 2-cyano-4'-[2''-propyl-4''-methyl-6''-(1'''methylbenzimidazol-2'''-yl)benzimidazol-1''-ylmethyl]biphenyl. The latter was hydrolyzed with KOH in ethylene glycol/H2O at 160° for 13.5 h to give after acidification with HCl, 98.2% Telmisartan hydrochloride.

IT **144702-27-2P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Telmisartan by reaction of propyldimethylbenzimidazolylbenzimidazole with bromomethylcyanobiphenyl followed by hydrolysis)

RN 144702-27-2 HCAPLUS

CN [1,1'-Biphenyl]-2-carbonitrile, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:651352 HCAPLUS
DOCUMENT NUMBER: 117:251352
TITLE: Preparation of N-biphenylylbenzimidazoles as angiotensin II antagonists
INVENTOR(S): Hauel, Norbert; Narr, Berthold; Ries, Uwe; Van Meel, Jacques; Wienen, Wolfgang; Entzeroth, Michael
PATENT ASSIGNEE(S): Thomae, Dr. Karl, G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 67 pp.

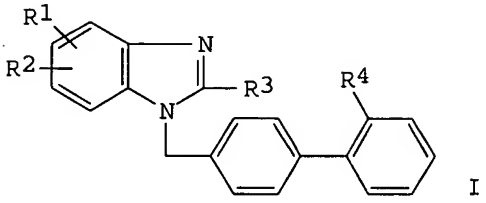
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 502314 | A1 | 19920909 | EP 1992-101579 | 19920131 |
| EP 502314 | B1 | 19980520 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE | | | | |
| DE 4103492 | A1 | 19921008 | DE 1991-4103492 | 19910206 |
| DE 4117121 | A1 | 19921217 | DE 1991-4117121 | 19910525 |
| DE 4137812 | A1 | 19930519 | DE 1991-4137812 | 19911116 |
| AT 166346 | E | 19980615 | AT 1992-101579 | 19920131 |
| ES 2118095 | T3 | 19980916 | ES 1992-101579 | 19920131 |
| CA 2060624 | AA | 19920807 | CA 1992-2060624 | 19920204 |
| CA 2060624 | C | 19991221 | | |
| IL 100864 | A1 | 19960119 | IL 1992-100864 | 19920204 |
| SK 279261 | B6 | 19980805 | SK 1992-306 | 19920204 |
| CZ 287607 | B6 | 20010117 | CZ 1992-306 | 19920204 |
| FI 9200486 | A | 19920807 | FI 1992-486 | 19920205 |
| FI 105547 | B1 | 20000915 | | |
| NO 9200476 | A | 19920807 | NO 1992-476 | 19920205 |
| NO 301585 | B1 | 19971117 | | |
| AU 9210707 | A1 | 19920813 | AU 1992-10707 | 19920205 |
| AU 655794 | B2 | 19950112 | | |
| HU 60493 | A2 | 19920928 | HU 1992-355 | 19920205 |
| HU 217084 | B | 19991129 | | |
| JP 04346978 | A2 | 19921202 | JP 1992-19852 | 19920205 |
| ZA 9200816 | A | 19930705 | ZA 1992-816 | 19920205 |
| RU 2053229 | C1 | 19960127 | RU 1992-5010824 | 19920205 |
| PL 169675 | B1 | 19960830 | PL 1992-293387 | 19920205 |
| KR 218820 | B1 | 19990901 | KR 1992-1730 | 19920206 |
| HR 940752 | B1 | 20010228 | HR 1994-940752 | 19941025 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 1991-4103492 | A | 19910206 |
| DE 1991-4117121 | A | 19910525 |
| DE 1991-4137812 | A | 19911116 |
| YU 1992-98 | A6 | 19920130 |
| CS 1992-306 | A | 19920204 |

OTHER SOURCE(S): MARPAT 117:251352
GI




I

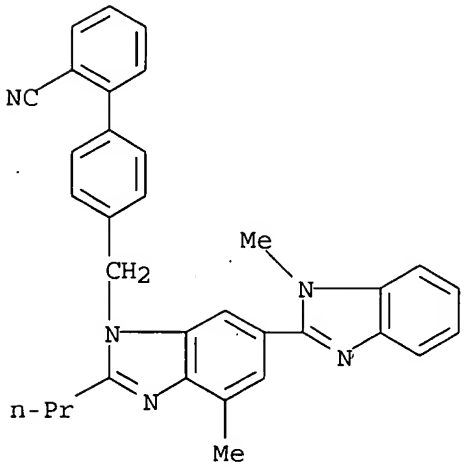
AB Title compns. (I; R1 = H, F, Cl, Br, alkyl,, FCH2, F2CH, F3C; R2 = imidazolylalkoxy, alkylsulfonyloxy, acylamino, phthalimido, amidino, (substituted) heteroaryl, etc.; R3 = H, (O- or S-interrupted) alkyl, cycloalkyl; R4 = CO2H, cyano, (1-triphenylmethyl)tetrazolyl, alkoxycarbonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl,

trifluoromethanesulfonylaminocarbonyl; with numerous provisos] were prepared Thus, tert-Bu 4'-[[2-butyl-7-[5-(imidazol-1-yl)pentyloxy]-4-methylbenzimidazol-1-yl]methyl]biphenyl-2-carboxylate was stirred with CF3CO2H in CH2Cl2 to give 29.9% free acid. I bound to the rat lung angiotensin II receptors with IC50 = 1.2-510.0 nM.

IT **144702-27-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of angiotensin II antagonists)

RN 144702-27-2 HCAPLUS

CN [1,1'-Biphenyl]-2-carbonitrile, 4'-[[1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl]methyl]- (9CI) (CA INDEX NAME)

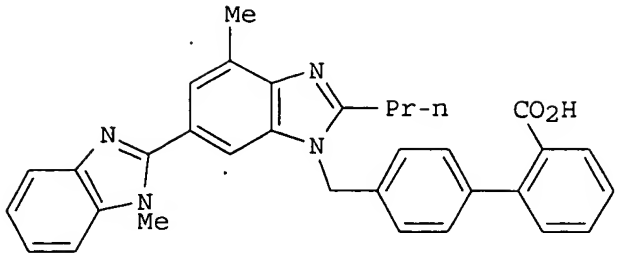



=> d l25 ibib abs hitstr tot

L25 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:568830 HCAPLUS
DOCUMENT NUMBER: 143:211912
TITLE: Preparation of telmisartan salt
INVENTOR(S): Zhong, Jingfen; Meng, Xiaodi; Guo, Yekun
PATENT ASSIGNEE(S): Shanghai Inst. of Medicine Industry, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. given
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 1548421 | A | 20041124 | CN 2003-117087 | 20030522 |

PRIORITY APPLN. INFO.: CN 2003-117087 20030522
OTHER SOURCE(S): CASREACT 143:211912
GI




I

AB The preparation of telmisartan salt I•M (M = Na, K, Ca, Mg, Me3NH2, amino acid, alkylamine) includes the reaction of telmisartan with organic alkali, inorg. alkali, arginine or lysine in organic solvent or water at -20~-150 °C for 1-30 h to produce target product salt. The pharmaceutical formulations of telmisartan salt were also presented.

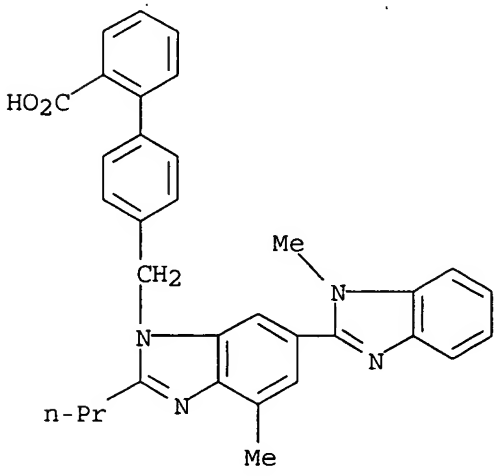
IT **862286-67-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of telmisartan salt and its pharmaceutical formulations)

RN 862286-67-7 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, compd. with 2-methyl-2-propanamine (1:1) (9CI) (CA INDEX NAME)

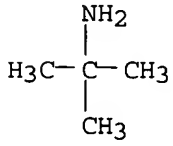
CM 1

CRN 144701-48-4
CMF C33 H30 N4 O2




CM 2

CRN 75-64-9
CMF C4 H11 N



L25 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:232614 HCAPLUS
DOCUMENT NUMBER: 142:291385
TITLE: Use of telmisartan and other agents for the prevention of migraine or other vascular headache
INVENTOR(S): Davidai, Giora
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005023250 | A1 | 20050317 | WO 2004-EP9709 | 20040901 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2005065094 | A1 | 20050324 | US 2004-925788 | 20040824 |
| PRIORITY APPLN. INFO.: | | | US 2003-500817P | P 20030905 |

AB The invention discloses a method for the prophylaxis of vascular headaches which do not originate from hypertension, especially migraine, the method comprising administration of telmisartan to a subject in need of such a treatment. The invention also discloses a method for the prophylaxis of vascular headaches, comprising the co-administration of telmisartan in combination with other drugs, e.g. triptans, suitable for migraine prophylaxis and/or acute treatment of migraine.

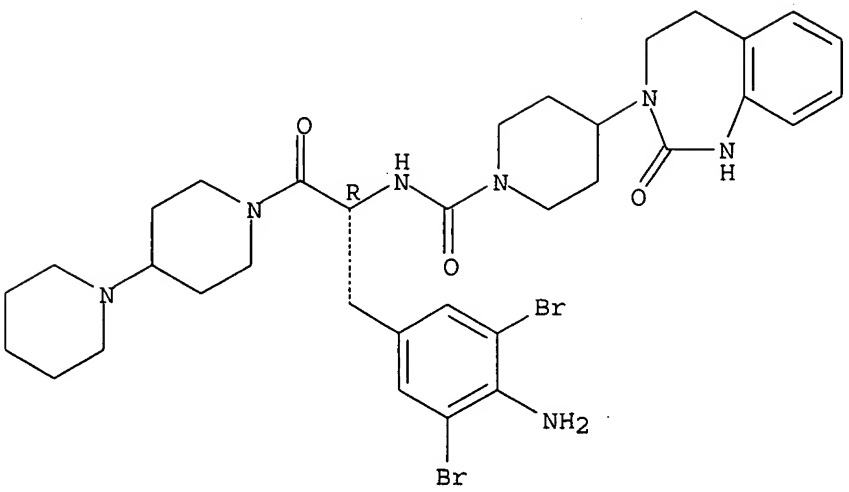
IT **847652-45-3**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(telmisartan and other agents for prevention of migraine or other vascular headache)

RN 847652-45-3 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-, mixt. with N-[(1R)-1-[(4-amino-3,5-dibromophenyl)methyl]-2-[1,4'-bipiperidin]-1'-yl-2-oxoethyl]-4-(1,2,4,5-tetrahydro-2-oxo-3H-1,3-benzodiazepin-3-yl)-1-piperidinecarboxamide (9CI) (CA INDEX NAME)

CM 1

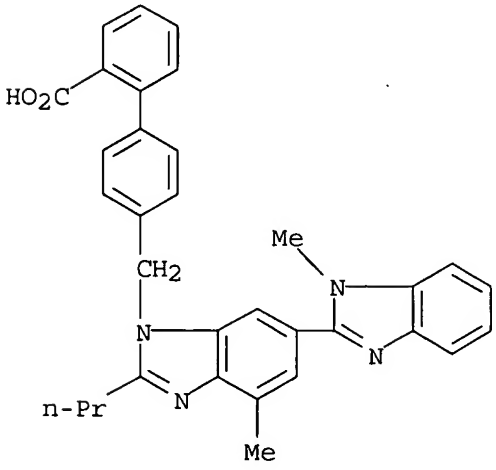
CRN 204696-59-3
CMF C34 H45 Br2 N7 O3

Absolute stereochemistry.



CM 2

CRN 144701-48-4
CMF C33 H30 N4 O2



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:610104 HCAPLUS
DOCUMENT NUMBER: 141:134092
TITLE: Telmisartan-simvastatin combination for the prophylaxis or treatment of cardiovascular, cardiopulmonary, pulmonary, or renal diseases

INVENTOR(S): Riedel, Axel; Sendra, Josep-Maria; Leiter, Josef M. E.; Kauschke, Stefan; Mark, Michael
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma GmbH & Co. Kg
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004062729 | A1 | 20040729 | WO 2004-EP175 | 20040114 |
| WO 2004062729 | C1 | 20041007 | | |
| W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA | | | | |
| DE 10301372 | A1 | 20040729 | DE 2003-10301372 | 20030116 |
| DE 10335027 | A1 | 20050217 | DE 2003-10335027 | 20030731 |
| CA 2513281 | AA | 20040729 | CA 2004-2513281 | 20040114 |
| US 2004259925 | A1 | 20041223 | US 2004-757295 | 20040114 |
| EP 1587584 | A1 | 20051026 | EP 2004-701918 | 20040114 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 2003-10301372 | A | 20030116 |
| DE 2003-10335027 | A | 20030731 |
| DE 2003-10301371 | A | 20030116 |
| US 2003-446695P | P | 20030211 |
| US 2003-503317P | P | 20030916 |
| WO 2004-EP175 | W | 20040114 |


AB The invention discloses a method for the prophylaxis or treatment of cardiovascular, cardiopulmonary, pulmonary or renal diseases, achieved by the improvement of endothelial function and the protection of organs, tissues and vessels when indications require a blood pressure check and a lipid level check, especially in patients that have been diagnosed with type 2 diabetes mellitus or if prediabetes is suspected. The method is also used for preventing diabetes and prediabetes and for the treatment of metabolic syndrome and insulin resistance in patients with normal blood pressure. The method involves the combined administration of effective quantities of telmisartan, or a polymorph or salt thereof, and simvastatin. The invention also discloses suitable pharmaceutical compns. containing telmisartan, or a polymorph or salt thereof, and simvastatin, as a combined preparation for simultaneous, sep., or sequential use in the prophylaxis or treatment of the above diseases. Preparation of the sodium salt of telmisartan is described.

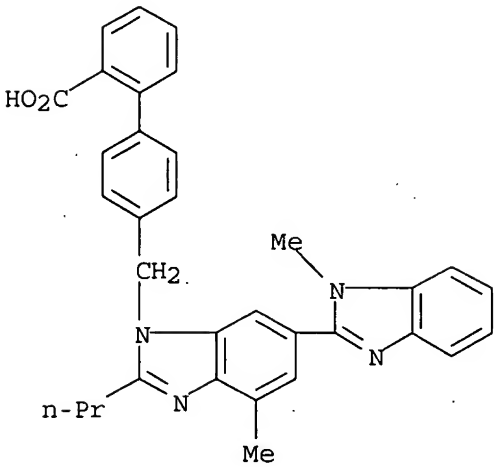
IT **725726-25-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(telmisartan-simvastatin combination for prophylaxis and treatment of cardiovascular, cardiopulmonary, pulmonary, and renal diseases)

RN 725726-25-0 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(3,7'-dimethyl-2'-propyl[2,5'-bi-3H-benzimidazol]-3'-yl)methyl]-, sodium salt, mixt. with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (9CI) (CA INDEX NAME)

CM 1

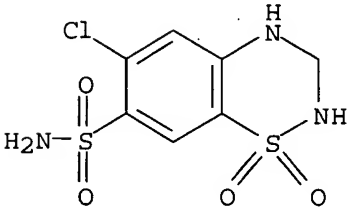
CRN 515815-47-1
CMF C33 H30 N4 O2 . Na



● Na

CM 2

CRN 58-93-5
CMF C7 H8 Cl N3 O4 S2



L25 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:606351 HCAPLUS
DOCUMENT NUMBER: 141:134089
TITLE: Telmisartan-atorvastatin combination for the prophylaxis or treatment of cardiovascular, cardiopulmonary, pulmonary, or renal diseases
INVENTOR(S): Riedel, Axel; Sendra, Josep-Maria; Leiter, Josef M. E.; Kauschke, Stefan; Mark, Michael
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma GmbH & Co. Kg
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004062557 | A2 | 20040729 | WO 2004-EP174 | 20040114 |
| WO 2004062557 | A3 | 20040916 | | |
| W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA | | | | |
| DE 10301371 | A1 | 20040805 | DE 2003-10301371 | 20030116 |
| DE 10335027 | A1 | 20050217 | DE 2003-10335027 | 20030731 |
| CA 2513277 | AA | 20040729 | CA 2004-2513277 | 20040114 |
| US 2004259925 | A1 | 20041223 | US 2004-757295 | 20040114 |
| EP 1587479 | A2 | 20051026 | EP 2004-701904 | 20040114 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 2003-10301371 | A | 20030116 |
| DE 2003-10335027 | A | 20030731 |
| US 2003-446695P | P | 20030211 |
| US 2003-503317P | P | 20030916 |
| WO 2004-EP174 | W | 20040114 |

AB The invention discloses a method for the prophylaxis or treatment of cardiovascular, cardiopulmonary, pulmonary, or renal diseases, achieved by the improvement of endothelial function and the protection of organs, tissues and vessels when indications require a blood pressure check and a lipid level check, especially in patients that have been diagnosed with type 2 diabetes mellitus or if prediabetes is suspected. The method is also used for preventing diabetes and prediabetes and for the treatment of metabolic syndrome and insulin resistance in patients with normal blood pressure. The method involves the combined administration of effective amts. of telmisartan, or a polymorph or salt thereof, and atorvastatin. The invention also discloses suitable pharmaceutical compns. containing telmisartan, or a polymorph or salt thereof, and atorvastatin, as a combined preparation for simultaneous, sep. or sequential use in the prophylaxis or treatment of the above diseases. Preparation of the sodium salt of telmisartan is described.

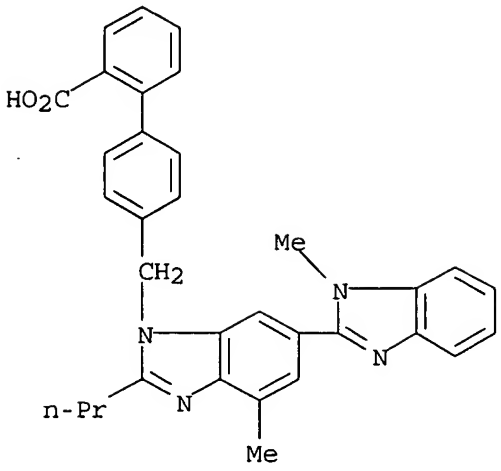
IT **725726-25-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(telmisartan-atorvastatin combination for prophylaxis and treatment of cardiovascular, cardiopulmonary, pulmonary, and renal diseases)

RN 725726-25-0 HCAPLUS

CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[(3,7'-dimethyl-2'-propyl[2,5'-bi-3H-benzimidazol]-3'-yl)methyl]-, sodium salt, mixt. with 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (9CI) (CA INDEX NAME)

CM 1

CRN 515815-47-1
CMF C33 H30 N4 O2 . Na



● Na

CM 2

CRN 58-93-5
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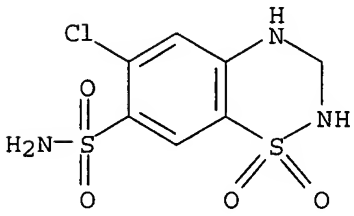

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|---|---|---|
| FULL ESTIMATED COST | 49.28 | 1103.52 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -5.11 | -39.42 |

STN INTERNATIONAL LOGOFF AT 14:31:05 ON 30 OCT 2005